JG17 Rec'd PCT/PTO 30 APR 2001

FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: GJE-65

U S APPLICATION NO (If known, see 37 CFR 1 5): 09/830807

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/03721	09 Nov 1999	09 Nov 1998 (See #20 below)

TITLE OF INVENTION: Virulence Genes And Proteins, And Their Use

APPLICANT(S) FOR DO/EO/US: Helen Rachel Crooke, Enda Elizabeth Clarke, Paul Howard Everest, Gordon Dougan, David William Jacqueline Elizabeth Shea and Robert Graham Feldman

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☑ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☑ Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☑ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)), unsigned.
10. ☐ An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☑ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 37 CFR 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☑ Other items or information:

Further priority dates: 17 December 1998; 13 January 1999; and 28 January 1999.

JC08 Rec'd PCT/PTO 30 APR 2001

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/830807	PCT/GB99/03721	GJE-65

21. ☑ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	22 - 20 =	2	x **$18.00**	$36.00	
Independent claims	8 - 3 =	5	x **$80.00**	$400.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$1,296.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$0.00	
SUBTOTAL =				$1,296.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$0.00	
TOTAL NATIONAL FEE =				$1,296.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$0.00	
TOTAL FEES ENCLOSED =				$1,296.00	
				Amount to be refunded:	$
				charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 19-0065 in the amount of $ 1,296.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0065 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

CORRESPONDENCE ADDRESS:

CUSTOMER NUMBER
23,557

Glenn P. Ladwig
SIGNATURE

April 30, 2001
DATE

Glenn P. Ladwig
NAME

46,853
REGISTRATION NUMBER

09/830807
JC08 Rec'd PCT/PTO 30 APR 2001

April 30, 2001

Patent Application
Docket No. GJE-65

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Helen Rachel Crooke, Enda Elizabeth Clarke, Paul Howard Everest, Gordon Dougan, David William Holden, Jacqueline Elizabeth Shea, Robert Graham Feldman

Docket No. : GJE-241

For : Hydroxamic And Carboxylic Acid Derivatives having MMP and TNF Inhibitory Activity

PRELIMINARY AMENDMENT

Please amend the above-identified patent application as follows:

In the Specification

After page 17: Please insert as new page 18 the attached Abstract of the Disclosure.

In the claims

The following amendments are made with respect to the claims in the international application PCT/GB99/03721 attached as Annexes to the International Preliminary Examination Report (IPER). Therefore, please replace existing page 17 of the international application with the amended claim sheet (replacement page 17) of the annex attached to the IPER, and make the following amendments to the pending claims so that they read as follows:

Claim 1 (amended):

An isolated peptide encoded by an operon, wherein said operon comprises a gene selected from the group consisting of *tatA*, *tatB, tatC, tatE, mdoG, creC, recG, yggN, eckl, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 2 (amended):

The isolated peptide, according to claim 1, comprising an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

Claim 3 (amended):

An isolated polynucleotide which comprises a gene selected from the group consisting of *tatA*, *tatB, tatC, tatE, mdoG, creC, recG, yggN, eckl, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 4 (amended):

A host transformed to express a peptide encoded by an operon, wherein said operon comprises a gene selected from the group consisting of *tatA*, *tatB, tatC, tatE, mdoG, creC, recG, yggN, eckl, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a

homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 5 (amended):

A vaccine comprising a peptide, or the means for its expression, wherein said peptide is encoded by an operon, wherein said operon comprises a gene selected from the group consisting of *tatA*, *tatB*, *tatC*, *tatE*, *mdoG*, *creC*, *recG*, *yggN*, *eck1*, *iroD*, *iroC*, *iroE*, *mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 6 (amended):

A vaccine comprising a microorganism having a virulence gene mutation, wherein the gene is selected from the group consisting of *tatA*, *tatB*, *tatC*, *tatE*, *mdoG*, *creC*, *recG*, *yggN*, *eck1*, *iroD*, *iroC*, *iroE*, *mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 7 (amended):

The vaccine, according to claim 6, wherein said virulence gene mutation comprises a virulence gene deletion in two genes, wherein one gene encodes *tatA* and the other encodes *tatE*.

Claim 8 (amended):

The vaccine, according to claim 6, wherein the gene lies within a pathogenicity island.

Claim 9 (amended):

A method for screening potential drugs, or for the detection of virulence, wherein said method utilizes a peptide encoded by an operon, wherein said operon comprises a gene selected from the group consisting of *tatA*, *tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 10 (amended):

A method for treatment or prevention of a condition associated with infection by a Gram-negative bacterium, said method comprising administering a vaccine to a person or animal in need thereof, wherein said vaccine comprises a peptide, or a host transformed to express said peptide, wherein said peptide is encoded by an operon comprising a gene selected from the group consisting of *tatA*, *tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 11 (amended):

The method, according to claim 10, wherein the bacterium is *E. coli*.

Please add the following new claims:

12. The polynucleotide, according to claim 3, wherein said gene encodes a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

13. The host, according to claim 4, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

14. The vaccine, according to claim 5, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

15. The vaccine, according to claim 6, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

16. The vaccine, according to claim 15, wherein said virulence gene mutation comprises a virulence gene deletion in two genes, wherein one gene encodes *tatA* and the other encodes *tatE*.

17. The vaccine, according to claim 15, wherein the gene lies within a pathogenicity island.

18. The method, according to claim 9, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

19. The method, according to claim 9, wherein said peptide comprises an amino acid sequence as set forth in SEQ ID NO. 33.

20. The method, according to claim 10, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

21. The method, according to claim 20, wherein the bacterium is *E. coli.*

22. A method for treatment or prevention of a condition associated with infection by a Gram-negative bacterium, said method comprising administering a nucleotide to a person or animal in need thereof, wherein said nucleotide comprises an operon including a gene selected from the group consisting of *tatA, tatB, tatC, tatE, mdoG, creC, recG, yggN, eckl, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

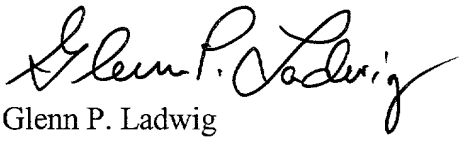
Remarks

Claims 1-11 have been amended and new claims 12-22 have been added.

No new matter has been added by these amendments.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Respectfully Submitted



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Marked-up Version of Amended Claims

Claim 1 (amended):

[A] An isolated peptide encoded by an operon, [including any of the genes identified herein as] wherein said operon comprises a gene selected from the group consisting of *tatA*, *tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to [16] *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, [having] wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof[, for therapeutic use].

Claim 2 (amended):

[A] The isolated peptide, according to claim 1, comprising [any of the amino acid sequences identified herein as] an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

Claim 3 (amended):

[A] An isolated polynucleotide [encoding a peptide according to claim 1 or claim 2, for therapeutic use] which comprises a gene selected from the group consisting of *tatA, tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 4 (amended):

A host transformed to express a peptide [according to claim 1 or claim 2] encoded by an operon, wherein said operon comprises a gene selected from the group consisting of *tatA, tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 5 (amended):

A vaccine comprising a peptide [according to claim 1 or claim 2], or the means for its expression, wherein said peptide is encoded by an operon, wherein said operon comprises a gene selected from the group consisting of *tatA, tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 6 (amended):

A vaccine comprising a microorganism having a virulence gene mutation, wherein the gene is selected from the group consisting of *tatA, tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof [according to claim 1 or claim 2].

Claim 7 (amended):

[A] The vaccine, according to claim 6, [having] wherein said virulence gene mutation comprises a virulence gene deletion in two genes, wherein one gene encodes *tatA* and the other encodes *tatE*.

Claim 8 (amended):

[A] The vaccine, according to claim 6, wherein the gene lies within a pathogenicity island[, wherein the island comprises a gene identified herein].

Claim 9 (amended):

[Use of a product according to any of claims 1 to 4, or SEQ ID NO. 33,] A method for screening potential drugs, or for the detection of virulence, wherein said method utilizes a peptide encoded by an operon, wherein said operon comprises a gene selected from the group consisting of *tatA, tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 10 (amended):

[Use of a product according to any of claims 1 to 4, for the manufacture of a medicament for use in the] A method for treatment or prevention of a condition associated with infection by a Gram-negative bacterium, said method comprising administering a vaccine to a person or animal in need thereof, wherein said vaccine comprises a peptide, or a host transformed to express said

peptide, wherein said peptide is encoded by an operon comprising a gene selected from the group consisting of *tatA, tatB, tatC, tatE, mdoG, creC, recG, yggN, eck1, iroD, iroC, iroE, mtd2*, and *ms1* to *ms16*, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, wherein said homologue has at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof.

Claim 11 (amended):

[Use] The method, according to claim 10, wherein the bacterium is *E. coli*.

VIRULENCE GENES AND PROTEINS, AND THEIR USE

Field of the Invention

This invention relates to the identification of virulence genes and proteins, and their use. More particularly, it relates to their use in therapy and in screening for drugs.

Background to the Invention

E. coli is a member of the *Enterobacteriaceae*, or enteric bacteria, which are Gram-negative microorganisms that populate the intestinal tracts of animals. Other members of this bacterial family include *Enterobacter*, *Klebsiella*, *Salmonella*, *Shigella* and *Yersinia*. Although *E. coli* is found normally in the human gastrointestinal tract, it has been implicated in human disease, including septicaemia, meningitis, urinary tract infection, wound infection, abscess formation, peritonitis and cholangitis.

The disease states caused by *E. coli* are dependent upon certain virulence determinants. For example, *E. coli* has been implicated in neonatal meningitis and a major determinant of virulence has been identified as the K1 antigen, which is a homopolymer of sialic acid. The K1 antigen may have a role in avoiding the host's immunological system and preventing phagocytosis.

Summary of the Invention

The present invention is based on the identification of a series of virulence genes in *E. coli* K1, and also related organisms the products of which may be implicated in the pathogenicity of the organism.

According to one aspect of the present invention, a peptide is encoded by an operon including any of the genes identified herein as *mdoG*, *creC*, *recG*, *yggN*, *tatA*, *tatB*, *tatC*, *tatE*, *eck1*, *iroD*, *iroC*, *iroE*, *mtd*2 and *ms*1 to 16, from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, or a functional fragment thereof. Such a peptide is suitable for therapeutic use, e.g. when isolated.

The term "functional fragments" is used herein to define a part of the gene or peptide which retains similar therapeutic utility as the whole gene or peptide. For example, a functional fragment of the peptide may be used as an antigenic determinant, useful in a vaccine or in the production of antibodies.

A gene fragment may be used to encode the active peptide. Alternatively, the gene fragment may have utility in gene therapy, targetting the wild-type gene *in vivo* to exert a therapeutic effect.

A peptide according to the present invention may comprise any of the amino acid sequences identified herein as SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 23, 24, 25, 26, 28, 31, 29, 32 and 35-48.

The identification of these peptides as virulence determinants allows them to be used in a number of ways in the treatment of infection. For example, a host may be transformed to express a peptide according to the invention or modified to disrupt expression of the gene encoding the peptide. A vaccine may also comprise a peptide according to the invention, or the means for its expression, for the treatment of infection. In addition, a vaccine may comprise a microorganism having a virulence gene deletion, wherein the gene encodes a peptide according to the invention.

According to another aspect of the invention, the peptides or genes may be used for screening potential antimicrobial drugs or for the detection of virulence.

A further aspect of this invention is the use of any of the products identified herein, for the treatment or prevention of a condition associated with infection by a Gram-negative bacterium, in particular by *E. coli*.

Description of the Invention

The present invention has made use of signature-tagged mutagenesis (STM) (Hensel *et al*, Science, 1995;269:400-403) to screen *E. coli* K1 strain RS228 (Pluschke *et al*, Infection and Immunity 39:599-608) mini-Tn5 mutant bank for attenuated mutants, to identify virulence genes (and virulence determinants) of *E. coli*.

Although *E. coli* K1 was used as the microorganism to identify the virulence genes, corresponding genes in other enteric bacteria are considered to be within the scope of the present invention. For example, corresponding genes or encoded proteins may be found, based on sequence homology, in *Enterobacter*, *Klebsiella* and other genera implicated in human intestinal disease, including *Salmonella*, *Shigella* and *Yersinia*.

The term "virulence determinant" is used herein to define a product, e.g. a peptide or protein that may have a role in the maintenance of pathogenic bacteria. In particular, a virulence determinant is a bacterial protein or peptide that is implicated in the pathogenicity of the infectious or disease-causing microorganism.

A gene that encodes a virulence determinant may be termed a "virulence gene". Disruption of a virulence gene by way of mutation, deletion or insertion, will result in a reduced level of survival of the bacteria in a host, or a general reduction in the pathogenicity of the microorganism.

Signature-tagged mutagenesis has proved a very useful technique for identifying virulence genes, and their products. The technique relies on the ability of transposons to insert randomly into the genome of a microorganism, under permissive conditions. The transposons are individually marked for easy identification, and then introduced separately into a microorganism, resulting in disruption of the genome. Mutated microorganisms with reduced virulence are then detected by negative selection and the genes where insertional inactivation has occurred are identified and characterised.

A first stage in the STM process is the preparation of suitable transposons or transposon-like elements. A library of different transposons are prepared, each being incorporated into a vector or plasmid to facilitate transfer into the microorganism. The preparation of vectors with suitable transposons will be apparent to a skilled person in the art and is further disclosed in WO-A-96/17951. For the Gram-negative bacteria, e.g. *E. coli*, suitable transposons include Tn5 and Tn10. Having prepared the transposons, mutagenesis of a bacterial strain is then carried out to create a library of individually mutated bacteria.

Pools of the mutated microorganisms are then introduced into a suitable host. After a suitable length of time, the microorganisms are recovered from the host and those microorganisms that have survived in the host are identified, thereby also identifying the mutated strains that failed to survive, i.e. avirulent strains. Corresponding avirulent strains in a stored library are then used to identify the genes where insertional inactivation occurred. Usually, the site of

transposon insertion is identified by isolating the DNA flanking the transposons insertion site, and this permits characterisation of the genes implicated in virulence.

Once an avirulent microorganism has been identified, it is possible to determine more fully the potential role of the mutated gene in virulence, by infecting a suitable host animal with a lethal dose of the mutant. The survival time of the infected animal is compared with that of a control infected with the wild-type strain, and those animals surviving for longer periods than the control may be said to be infected with microorganisms having mutated virulence genes.

Alternatively, the potential role in virulence can be investigated by infecting an animal host with a mixture of the wild-type and mutant bacteria. After a suitable period of time, bacteria are harvested from organs of the host animal and the ratio of wild-type and mutant bacteria determined. This ratio is divided by the ratio of mutant to wild-type bacteria in the inoculum, to determine the competitive index (CI). Mutants which have a competitive index of less than 1 may be said to be avirulent.

It is possible that the gene which is inactivated by the insertion of the transposon may not be a true virulence gene, but may be having a polar effect on a downstream (virulence) gene. This can be determined by further experimentation, placing non-polar mutations in more defined regions of the gene, or mutating other adjacent genes, and establishing whether or not the mutant is avirulent.

Having characterised a virulence gene in *E. coli*, it is possible to use the gene sequence to establish homologies in other microorganisms. In this way it is possible to determine whether other microorganisms have similar virulence determinants. Sequence homologies may be established by searching in existing databases, e.g. EMBL or Genbank.

Virulence genes are often clustered together in distinct chromosomal regions called pathogenicity islands. Pathogenicity islands can be recognised as they are usually flanked by repeat sequences, insertion elements or tRNA genes. Also the G+C content is normally different from the remainder of the

chromosome, suggesting that they were acquired by horizontal transmission from another organism. For example the G+C content of the *E. coli* K12 genome is 52%. Any pathogenicity islands found in *E. coli* strains are likely to have a G+C content that varies from this average.

The identified virulence genes are likely to be useful both in generating attenuated vaccine strains and as a target for antimicrobials. The same may be true for homologues in Gram-negative bacteria in general.

For the purpose of this invention, the appropriate degree of homology is typically at least 30%, preferably at least 50%, 60% or 70%, and more preferably at least 80% or 90% (at the amino acid or nucleotide level).

Proteins according to the invention may be purified and isolated by methods known in the art. In particular, having identified the gene sequence, it will be possible to use recombinant techniques to express the genes in a suitable host. Active fragments and homologues can be identified and may be useful in therapy. For example, the proteins or their active fragments may be used as antigenic determinants in a vaccine, to elicit an immune response. They may also be used in the preparation of antibodies, for passive immunisation, or diagnostic applications. Suitable antibodies include monoclonal antibodies, or fragments thereof, including single chain fv fragments. Methods for the preparation of antibodies will be apparent to those skilled in the art.

The preparation of vaccines based on attenuated microorganisms is known to those skilled in the art. Vaccine compositions can be formulated with suitable carriers or adjuvants, e.g. alum, as necessary or desired, and used in therapy, to provide effective immunisation against *E. coli* or other Gram-negative bacteria. The preparation of vaccine formulations will be apparent to the skilled person.

More generally, and as is well known to those skilled in the art, a suitable amount of an active component of the invention can be selected, for therapeutic use, as can suitable carriers or excipients, and routes of administration. These factors will be chosen or determined according to known criteria such as the

nature/severity of the condition to be treated, the type or health of the subject etc.

The following Examples illustrate the invention. For the Examples, STM was used to screen an *E. coli* K1 mini-Tn5 mutant bank for attenuated mutants, using a mouse model of systemic infection. The basic procedure followed that disclosed in Hensel *et al*, *supra*. *E. coli* K1 containing a mini-Tn5 insertion within a virulence gene was not recovered from mice inoculated with a mixed population of mutants, and is therefore likely to be attenuated.

The DNA region flanking either side of the mini-Tn5 insertion was cloned by inverse PCR or by rescue of a kanamycin-resistance marker. In the latter case, chromosomal DNA from the STM-derived mutant was digested with restriction enzymes, ligated into the plasmid pUC19, and kanamycin-resistant clones selected after transformation into competent *E. coli* K12 cells. Subsequent cloning and sequencing was then performed and the gene sequences compared using sequences in publicly available sequence databases (EMBL) to help characterise the putative gene products.

Example 1

In a first mutant, two fragments of cloned DNA were sequenced. The nucleotide sequences are shown as SEQ ID NO. 1 and SEQ ID NO. 3 and a translated region of the DNA from SEQ ID NO. 1 is shown as SEQ ID NO. 2. SEQ ID NO. 1 shows 99.8% identity to the *mdoGH* region from *E. coli* K12 (EMBL database accession number AE000206) from nucleotides 2577 to 6908. This DNA fragment encodes the 5'-part of the *ymdD* gene, the entire *mdoG* gene and the 5'-part of the *mdoH* gene. The product of the *mdoG* gene is of unknown function, but is believed to be involved in the biosynthesis of membrane-derived oligosaccharides.

SEQ ID NO. 3 shows 98.3% identity to the 3'-part of the *mdoH* gene and downstream gene sequences from *E. coli* K12 (nucleotides 7187 to 7760). SEQ ID NO. 2 shows 99.6% identity to the *mdoG* protein from *E. coli* K12 (Swiss Prot accession number P33136) at amino acid 1 to 511.

The novel gene was tested for attenuation of virulence, using mixed infections, in a murine model of systemic infection (Achtman *et al.*, Infection and

Immunity, 1983; Vol. 39:315-335), and shown to be attenuated with a competitive index (CI) of 0.38. This confirms that the attenuation of the original transposon mutant is likely to be due to the disruption of the *mdoG* gene.

Polar and a non-polar deletion mutants of *mdoG* were constructed. The *mdoG* gene and flanking regions were amplified by PCR with oligonucleotides 5'-TGCTCTAGAGCCATTACTCAGAATGGG-3' (SEQ ID NO. 49) and 5'-CGCGAGCTCGACGACTGAATGATCCC-3' (SEQ ID NO. 50). The product was cloned into pUC19. A PCR product containing 5'- and 3'-terminal fragments of *mdoG* and the entire pUC19 sequence was then amplified by inverse PCR with the oligonucleotides 5'-TCCCCCGGGTACTGCAGCACTCAACC-3' (SEQ ID NO. 51) and 5'-GATCCCGGGACCACTGAAATGCGTGC-3' (SEQ ID NO. 52). A non-polar kanamycin resistance cassette (*aphT*) was inserted in both orientations between the *mdoG* sequences to give a polar and a non-polar construct. The *mdoG::aphT* fusions were then transferred to the suicide vector pCDV442. The chromosomal copy of the *mdoG* was mutated by allelic transfer after conjugation of the pCDV442 constructs into wild type *E. coli* K1.

The contructed mutants were tested for attenuation of virulence in a murine model of systemic infection (Achtman et al., *supra)*. Both the polar and the non-polar constructs were attenuated in virulence, with competitive indices of 0.37 and 0.35, respectively (mean CI from three mice each). This confirms that the attenuation of the original transposon mutant is likely to be due to the disruption of the *mdoG* gene.

Example 2

A second mutant was identified with a virulence gene having the nucleotide sequence shown in SEQ ID NO. 4 and the translated amino acid sequence shown as SEQ ID NO. 5. The mini-Tn5 transposon inserted at nucleotide 581 (SEQ ID NO. 4) and at amino acid 187 (SEQ ID NO. 5).

These sequences show 97.9% identity to the *creC* gene of *E. coli* K12 (EMBL and Genbank accession numbers M13608, AE000510 and U14003).

The *creC* protein from *E. coli* K12 belongs to the protein family of histidine kinases as well as to a protein family consisting of proteins containing a signal domain.

The novel gene was tested for attenuation of virulence (Achtman *et al*, *supra*.), and shown to be attenuated with a competitive index of 0.09.

As the *E. coli* K12 *creC* gene is transcribed as part of an operon with the *creD* gene, it is possible that this attenuation is due to a polar effect on a presumed *E. coli* K1 *creD* gene.

Example 3

A third mutant had a nucleotide sequence shown as SEQ ID NO. 6 immediately following the mini-Tn5. A translation of this sequence is shown as SEQ ID NO. 7.

The nucleotide sequence shows 93.7% identity to the *recG* gene of *E. coli* K12, at nucleotides 5-146 (EMBL and Genbank accession numbers P24230 and M64367). This demonstrates that the disrupted gene is at least partially identical to the *recG* gene of *E. coli* K12. The *recG* gene of *E. coli* K12 encodes a 76.4kD protein which functions as ATP-dependent DNA helicase, and plays a critical role in DNA repair.

In tests for attenuation, the competitive index was shown to be 0.48. The *recG* gene is transcribed as the terminal gene of an operon, and it is therefore unlikely that this attenuation is due to a polar effect on another *E. coli* K1 gene.

Example 4

A fourth mutant had a transposon inserted within the nucleotide sequence shown as SEQ ID NO. 8, with a translation product shown as SEQ ID NO. 9.

The mini-Tn5 transposon inserted at nucleotide 359 and amino acid 80.

These sequences show 98.5% sequence identity to the *yggN* gene of *E. coli* K12 (EMBL accession number AE000378) at nucleotides 339-1054, and 99.6% identity at the amino acid level.

Although the sequence of the *yggN* gene is known, the function of its encoded protein has not yet been determined.

The novel gene was tested for attenuation of virulence, and shown to be attenuated with a competitive index of 0.43.

Example 5

Several mutants were also found with a transposon insertion within the same region. Cloning and sequencing the region revealed a nucleotide sequence shown as SEQ ID NO. 10. This sequence has homology with the *tatABCD* operon of *E. coli* K12 (EMBL and Genbank accession numbers AJ005830, AE000459 and AE000167). This operon encodes proteins of predicted mass 9.6 kD, 18.4 kD, 28.9 kD and 29.5 kD, which function as components of a Sec-independent protein export pathway. The pathway permits translocation of fully folded proteins to the periplasm through a gated pore, after the attachment of co-factors in the cytoplasm.

Translation of the nucleotide sequence revealed a protein corresponding to *tatA* (SEQ ID NO. 11), a sequence corresponding to *tatB* (SEQ ID NO. 12), a sequence corresponding to *tatC* (SEQ ID NO. 13) and a sequence corresponding to *tatD* (SEQ ID NO. 14).

The mini-Tn5 transposons in the mutants identified by STM are located at nucleotides 1429 and 2226 of SEQ ID NO. 10. These transposon insertions disrupt the *tatB* protein sequence at amino acid 50 and the *tatC* protein sequence at amino acid 143.

The *tatB* and *tatC* genes were tested for attenuation of virulence and were shown to be attenuated with competitive indices of 0.0012 and 0.0039, respectively. These genes were also attenuated in virulence when tested in single infections in the same model of systemic infection.

Example 6

A further mutant was insertionally inactivated within a region corresponding to the *tatE* gene of *E. coli* K12, shown as SEQ ID NO. 15. A translation of the sequence as shown as SEQ ID NO. 16. The *tatE* gene shows 98% identity to that of the *E. coli* K12 gene (accession number AE000167) at nucleotides 6719-7306.

To establish whether the *tatA, tatD* and *tatE* genes are required for virulence, non-polar deletion mutations were constructed in each. The regions of DNA flanking either side of the *tatA*, *tatD* and *tatE* genes were amplified with the following primers:

tatA

5'-TCG TCT AGA GAT GAT GGT GAT GGA GCG-3' (SEQ ID NO. 53)

5'-GAA CTG CAG CCA AAT ACT GAT ACC ACC C-3' (SEQ ID NO. 54)

5'-GAA CTG CAG GCT AAA ACA GAA GAC GCG-3' (SEQ ID NO. 55)

5'-CAT GCA TGC ACT CCA TAT GAC AAC CGC-3' (SEQ ID NO. 56)

Primers SEQ ID NO. 53 and SEQ ID NO. 54 were used to amplify DNA sequences upstream of *tatA*, Primers SEQ ID NO. 55 and SEQ ID NO. 56 were used to amplify DNA sequences downstream of *tatA*.

tatD

5'-TCG TCT AGA ATG AAG CTG CGC ATG AGG-3' (SEQ ID NO. 57)

5'-CAA CTG CAG TCG CAA ATT GCG AAC TGG-3' (SEQ ID NO. 58)

5'-CAA CTG CAG ACC GCA ACT TTT CGA CGC-3' (SEQ ID NO. 59)

5'-CAT GCA TGC CAG TGA GCC ATT GTT CCC-3' (SEQ ID NO. 60)

Primers SEQ ID NO. 57 and SEQ ID NO. 58 were used to amplify DNA sequences upstream of *tatD*, Primers SEQ ID NO. 59 and SEQ ID NO. 60 were used to amplify DNA sequences downstream of *tatD*.

tatE

5'-TGC TCT AGA TAC GAC TCT GAC AGG AGG-3' (SEQ ID NO. 61)

5'-TCA GAT ATC AAC TAC CAG CAG TTT GG-3' (SEQ ID NO. 62)

5'-TCA GAT ATC CAT AAA GAG TGA CGT GGC-3' (SEQ ID NO. 63)

5'-TGC TCT AGA AAA CGT GGC AAC AGA GCG-3' (SEQ ID NO. 64)

Primers SEQ ID NO. 61 and SEQ ID NO. 62 were used to amplify DNA sequences upstream of *tatE*, Primers SEQ ID NO. 63 and SEQ ID NO. 64 were used to amplify DNA sequences downstream of *tatE*.

After cloning these flanking DNA fragments into pUC19, a non-polar *aphT* kanamycin resistance cassette (Galan *et al*, J.Bacteriol, 1992;174:4338-4349) was inserted between the flanking DNA fragments to replace the *tatA*, *tatD* and *tatE* genes. These DNA fragments were then transferred to the suicide vector pCVD442 (Blomfield *et. al*, Mol. Micro., 1991;5:1447-1457). The chromosomal copies of the *E. coli* K1 *tatA*, *tatD* and *tatE* genes were then mutated by allelic transfer after conjugation of the pCVD442 constructs into wild type *E. coli* K1.

Disruptions of the *tatA*, *tatD* and *tatE* genes have been tested for attenuation of virulence (Achtman *et al.*, *supra*).

None of the genes was attenuated when deleted in isolation. The genes may still play a role in virulence, and to test this, mutants were prepared with deletions in both *tatA* and *tatE* genes. The double mutant was tested for attenuation in virulence using mixed infections with the wild-type strain and shown to be attenuated with a competitive index of 0.0017. It seems therefore that the *tatA, tatD* and *tatE* genes may be used in combination to create avirulent microorganisms.

Given the similarity of the *E. coli* K1 *tatABCD* genes to predicted *tatABCD* genes present in the *S. typhimurium* genome and *Neisseria meningitidis* genome it seemed likely that the tat system may also be required for virulence in these, and other, organisms. A deletion in the *S. typhimurium* *tatC* gene (SEQ ID NO. 17) was constructed by amplifying the DNA flanking either side of the *tatC* gene with the following primers:

5'-TGC TCT AGA AGG CGT TGT CGA TCC TG-3' (SEQ ID NO. 65)

5'-GAA CTG CAG GAA AAG GCC GAG CAG ACT G-3' (SEQ ID NO. 66)

5'-GAA CTG CAG TAC AGC CAT GTT TAC GGT-3' (SEQ ID NO. 67)

5'-CAT GCA TGC GGT GTA CGA CAG TTT GCG-3' (SEQ ID NO. 68)

Primers SEQ ID NO. 65 and SEQ ID NO. 66 were used to amplify DNA sequences downstream of the *S. typhimurium tatC* gene, Primers SEQ ID NO. 67 and SEQ ID NO. 68 were used to amplify DNA sequences upstream of the *S. typhimurium tatC* gene.

The encoded amino acid sequences for two regions of the tatC gene are shown as SEQ ID NO. 18 and SEQ ID NO. 19.

After cloning these flanking DNA fragments into pUC19, a non-polar kanamycin resistance cassette (*aphT*) was inserted between the flanking DNA fragments to replace the *S. typhimurium tatC* gene. This DNA fragment was then transferred to the suicide vector pCVD442. The chromosomal copy of the *S. typhimurium tatC* gene was then mutated by allelic transfer after conjugation of the pCVD442 construct into wild type *S. typhimurium* strains TML and SL1344.

The disrupted *S. typhimurium tatC* gene was tested for attenuation of virulence, using mixed and single infections in a murine model of systemic infection. For mixed infections, 6-7 week old *balbC* mice were inoculated intraperitoneally with 10^4 bacterial cells. Competitive indices were calculated after comparing the numbers of mutant and wild-type bacteria present in spleens after 3 days. For single infections, mice were inoculated either intraperitoneally or orally with varying doses and mouse survival monitored for 17 days. The strains were attenuated in virulence, the competitive indices of the SL1344 *tatC* and TML *tatC* deletion strains being 0.078 and 0.098, respectively.

In single infections, mouse survival was extended compared to the wild-type controls.

Sequence homology was also demonstrated with the tat sequence from *Neisseria meningitidis*. The gene sequence from *N. meningitidis* is shown as SEQ ID NO. 20 and the encoded amino acid sequence for tatC is shown as SEQ ID NO. 21.

To test for virulence, a deletion mutant was created using the following primers:

5'-TGCTCTAGACACATCATGGGCACACC-3' (SEQ ID NO. 69)

5'-GAACTGCAGAACCGTCCACATCAGGCG-3' (SEQ ID NO. 70)

5'-GAACTGCAGACCCTGCTTGCCATTCCG-3' (SEQ ID NO. 71)

5'-GAACTGCAGACCCTGCTTGCCATTCCG-3' (SEQ ID NO. 72)

Cloning of the DNA fragments and the *aphT* kanamycin resistance cassette into pUC19 followed the procedure outlined above for *S. typhimurium*. The chromosomal copy of the *N. meningitidis tatC* gene was mutated by transformation of the pUC19-based constructs into wild-type *N. meningitidis* cells.

Southern analysis of the resulting transformants indicated that all the transformants were merodiploids and contained both the wild-type and mutated copies of the *tatC* gene. This indicates that there is some selection against the isolation of mutants in which the *tatC* gene has been deleted.

Further studies on polar and non-polar constructs showed that transformants did not grow on selective media. This suggests that the *N. meningitidis tatC* gene is essential for the *in vitro* growth of this organism.

Example 7

A further mutant was identified with a transposon insertion within a nucleotide sequence identified herein as SEQ ID NO. 22, at nucleotide 3981. The sequence defined herein as *eck1*, shows sequence homology to several Group 1 glycosyltransferases from a number of bacteria. Sequence homology was also shown to the *gnd* gene of *E. coli* K12 (at nucleotides 4197-4604 of SEQ ID NO. 22).

The translation of the *E. coli eck1* gene is shown as SEQ ID NO. 26. The gene has been tested for attenuation of virulence, as described above, and is shown to be attenuated with a competitive index of 0.025.

Several open reading frames (ORF) were also identified from the DNA sequence (SEQ ID NO. 22). The first of these is defined herein as MS1 and a translation product shown as SEQ ID NO. 25. The amino acid sequence is shown to have 50.3% identity to a putative glycosyl transferase from *E. coli*

serotype 0111 (TrEMBL database accession number AAD46732). The amino acid sequence also shows homology with the eck1 protein from *E. coli* K1 and also the TrsE protein from *Yersinia entercolitica* (TrEMBL database accession number Q56917).

A second open reading frame identified herein as MS2 had the gene sequence shown as SEQ ID NO. 24. This shows sequence homology to the putative glycosyl transferase TrsC from *Yersinia entercolitica* (TrRMBL database accession number Q56915), and also the glycosyl transferase WbnA from *E. coli* serotype 0113 (TrEMBL database accession number AAD50485).

A third open reading frame encodes a product identified herein as MS3 (SEQ ID NO. 23). The amino acid sequence shows 30.2% identity to a rhamnosyltransferase from *Streptoccus mutans*.

The gene sequence shown as SEQ ID NO. 22 may be at least part of a pathogenicity island, with multiple virulence genes being positioned in a cluster on the microorganism's genome.

Example 8

A further mutant was identified having a transposon insertion within the *iroCDE* operon. The nucleotide sequences flanking either side of the mini-Tn5 insertion are shown as SEQ ID NO. 27 and SEQ ID NO. 30.

The mini-Tn5 transposon is inserted at nucleotide 1272 of SEQ ID NO. 27 and at nucleotide 1 of SEQ ID NO. 30, and interrupts the *iroD* gene. The N-terminal region of *iroD* is shown as SEQ ID NO. 29, and the C-terminal region is shown as SEQ ID NO. 31.

In addition to *iroD*, the gene shown as SEQ ID NO. 27 encodes a partial peptide with the amino acid sequence shown as SEQ ID NO. 28. This amino acid sequence shows 70.9% identity to the putative ATP binding cassette transporter *iroC* from *Salmonella typhi*.

The gene sequence shown as SEQ ID NO. 30 includes an open reading frame that encodes a peptide with the amino acid sequence shown as SEQ ID NO. 32 and this has sequence homology to the *iroE* protein from *Salmonella typhi*.

Testing the genes in a model for attenuation of virulence, as described above, showed that the *iroD* gene was attenuated with a competitive index of 0.107. The mini-Tn5 mutation in the iroD gene has been reintroduced into the wild-type *E. coli* K1 strain by P1 transduction. The resulting transductant is also attenuated in virulence with a competitive index of 0.1. This indicates that the attenuated phenotype is linked to the insertion within *iroD*. However, it is possible that the attenuation is due to a polar effect on the *E. coli* K1 *iroE* gene.

Example 9

A further mutant was identified with a transposon insertion within the nucleotide sequence shown as SEQ ID NO. 33. The transposon is inserted at nucleotide 2264 of SEQ ID NO. 33. The nucleotide sequence shows sequence homology to the *aslA / hemY* region of *E. coli* K12 (EMBL accession number AE000456). The *aslA* encodes an arylsulfatase homologue whereas *hemY* is involved in the biosynthesis of protoheme IX. This demonstrates that the disrupted region is at least partially identical to the *aslA / hemY* region of *E. coli* K12.

The transposon is inserted at nucleotide 2264 of SEQ ID NO. 33. This insertion site is 216 nucleotides downstream from the stop codon of the *hemY* gene and 472 nucleotides upstream from the start codon of the *aslA* gene.

The novel region has been tested for attenuation of virulence, as described above, and shown to be attenuated with a competitive index of 0.033. The mini-Tn5 mutation in this region has been reintroduced into the wild-type *E. coli* K1 strain by P1 transduction. The resulting transductant is also attenuated in virulence with a competitive index of 0.008. This indicates that the attenuated phenotype is linked to the transposon insertion in this region. However, polar and non-polar deletion mutants of *aslA* were constructed and tested for attenuation of virulence as described above.

Neither the polar nor the non-polar mutants were attenuated in virulence and this demonstrates that the attenuation of the original transposon mutant is not due to a polar effect on the *asl*A gene. This indicates that the transposon is disrupting some other function encoded within the intergenic region between *asl*A and *hem*Y. For example there could be some untranslated RNA molecule,

such as a regulatory RNA similar to oxyS (Altuvia *et al.*, Cell, 1997;90:43-53), encoded within this region. Alternatively the transposon could be disrupting some DNA structure that may, for example, be involved in DNA replication. This DNA region is also present in the pathogen *Salmonella typhimurium* suggesting that it may be important for pathogenicity in other organisms. This region (SEQ ID NO. 33) may be used as a target, to identify anti-microbial drugs.

Example 10

A further mutant was identified and the DNA region flanking either side of the mini-Tn5 insertion was cloned and had the nucleotide sequence shown as SEQ ID NO. 34. This nucleotide sequence has homology with the *mtd2* gene of *Herpetosiphon aurantiacus* (EMBL accession number P25265), with the *mtd2* gene product functioning as a cytosine-specific methyltransferase. The *mtd2* gene is not found in the *E. coli* K12 genome and may represent a pathogenicity island.

The mini-Tn5 transposon insertions were located at nucleotides 4773 and 3764 of SEQ ID NO. 34 and were shown to interrupt the *mtd2* gene.

The amino acid sequence of the *mtd2* gene is shown as SEQ ID NO. 43.

The *E. coli* K1 *mtd2* gene was tested for attenuation of virulence, as described above, and shown to be attenuated with a competitive index of 0.073.

In addition to the *mtd2* gene, a series of open reading frames were also identified with translation products identified herein as MS4 to MS16, SEQ ID NOS. 48-44 and 42-35, respectively. As the open reading frames are located in a potential pathogenicity island, mutations in these genes may also result in attenuation in virulence. Further, since it is known that *E. coli* and other bacteria may encode peptides in different forms in the nucleotide sequence, the coding regions of some of these proteins may overlap. In addition, any aminoacid sequence shown starting with Val may in fact start with Met.

CLAIMS

1. A peptide encoded by an operon including any of the genes identified herein as *tatA*, tatB, *tatC*, *tatE*, *mdoG*, *creC*, *recG*, *yggN*, *eck1*, *iroD*, *iroC*, *iroE*, *mtd*2 and *ms*1 to 16, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, having at least 30% homology at the amino acid or nucleotide level, or a functional fragment thereof, for therapeutic use.

2. A peptide according to claim 1, comprising any of the amino acid sequences identified herein as SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

3. A polynucleotide encoding a peptide according to claim 1 or claim 2, for therapeutic use.

4. A host transformed to express a peptide according to claim 1 or claim 2.

5. A vaccine comprising a peptide according to claim 1 or claim 2, or the means for its expression.

6. A vaccine comprising a microorganism having a virulence gene mutation, wherein the gene encodes a peptide according to claim 1 or claim 2.

7. A vaccine according to claim 6, having a virulence gene deletion in two genes, wherein one gene encodes *tatA* and the other encodes *tatE*.

8. A vaccine according to claim 6, wherein the gene lies within a pathogenicity island, wherein the island comprises a gene identified herein.

9. Use of a product according to any of claims 1 to 4, or SEQ ID NO. 33, for screening potential drugs or for the detection of virulence.

10. Use of a product according to any of claims 1 to 4, for the manufacture of a medicament for use in the treatment or prevention of a condition associated with infection by a Gram-negative bacterium.

11. Use according to claim 10, wherein the bacterium is *E. coli*.

09/830

Abstract of the Disclosure

The present invention is based on the identification of a series of virulence genes in *E. coli* K1, the products of which may be implicated in the pathogenicity of the organisms. The identification of the genes allows them, or their expressed products, to be used in a number of ways to treat infection.

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REP0592 US

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DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on an invention entitled
VIRULENCE GENES AND PROTEINS, AND THEIR USE

the specification of which ☐ is attached hereto or

☒ was filed on 09 NOV 1999 as United States Application Number or PCT International Application Number PCT/GB99/03721 and was amended on 21 JAN 2001 (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for a patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached? YES	NO
see attached sheet			☐	☐	☐
			☐	☐	☐
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Applicant:	Microscience Limited			
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

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Country of Citizenship: United Kingdom Date of signature: 9/5/01

6-00 Full name of Sixth Inventor: Jacqueline Elizabeth SHEA

Inventor's signature: [signature]

Residence address: London, United Kingdom GBX

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Country of Citizenship: United Kingdom Date of signature: 29/5/01

7-00

Full name of Seventh Inventor: Robert Graham FELDMAN

Inventor's signature: [signature]

Residence address: London, United Kingdom GBX

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Country of Citizenship: United Kingdom

Date of signature: 25 APR 2001

SEQUENCE LISTING

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His Asp Lys Ala Tyr Trp Asn Asn Leu Lys Thr Pro Phe Lys Leu Glu
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Phe Tyr His Gln Gly Met Tyr Phe Asp Thr Pro Val Lys Ile Asn Glu
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Asn Pro Gln Gly Phe Gly Leu Leu Gln Arg Gly Arg Asp Phe Ser Arg
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Pro Thr Asn Asp Glu Thr Asn Asp Asn Ile Val Ala Tyr Trp Thr Pro
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Asp Gln Leu Pro Glu Pro Gly Lys Glu Met Asn Phe Lys Tyr Thr Ile
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acc ttc agc cgt gat gaa gac aaa ctg cat gcg cca gat aac gca tgg   2219
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SUBSTITUTE SHEET (RULE 26)

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ttt gtc aaa gaa gtt aaa ccg ggc gtg cga aga gca acc gag ggg acg   147
Phe Val Lys Glu Val Lys Pro Gly Val Arg Arg Ala Thr Glu Gly Thr
                 30                  35                  40

tta atc gac acc gca acg ttg ctg gcg gag ctg gcg cgt ccc gat ttg   195
Leu Ile Asp Thr Ala Thr Leu Leu Ala Glu Leu Ala Arg Pro Asp Leu
             45                  50                  55

ctc tct ggg gac cca acg cat ggg caa ctg gcg cag gcg ttt aat cag   243
Leu Ser Gly Asp Pro Thr His Gly Gln Leu Ala Gln Ala Phe Asn Gln
         60                  65                  70

cta caa cat cgc ccg ttt cgc gcc aat atc ggt ggc att aac aaa gtg   291
Leu Gln His Arg Pro Phe Arg Ala Asn Ile Gly Gly Ile Asn Lys Val
     75                  80                  85

cgc aac gaa tat cat gtc tat atg acc gat gcg cag ggc aaa gta ttg   339
Arg Asn Glu Tyr His Val Tyr Met Thr Asp Ala Gln Gly Lys Val Leu
 90                  95                 100                 105

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Phe Asp Ser Ala Asn Lys Ala Val Gly Gln Asp Tyr Ser Arg Trp Asn
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Gln Asn Pro Ala Asp Pro Glu Ser Ser Val Met Tyr Val Ala Ala Pro
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Ile Met Asp Gly Ser Arg Leu Ile Gly Val Leu Ser Val Gly Lys Pro
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aac gcg gcg atg gct ccg gtc att aag cgt agc gag cgg cga att tta   579
Asn Ala Ala Met Ala Pro Val Ile Lys Arg Ser Glu Arg Arg Ile Leu
170                 175                 180                 185

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gat tcc gtc act gac aat aag ccc gtt cct ctc ccc gat ctc ggt agt   723
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Ser Glu Leu Arg Lys Leu Ala Gln Ala Leu Glu Ser Met Arg Val Lys
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ctg gaa ggg aaa aac tat att gag cag tat gtt tat gcg tta act cat   819
Leu Glu Gly Lys Asn Tyr Ile Glu Gln Tyr Val Tyr Ala Leu Thr His
250                 255                 260                 265

gag cta aaa agc cca ctg gcg gcg att cgt ggc gcg gcg gaa att tta   867
Glu Leu Lys Ser Pro Leu Ala Ala Ile Arg Gly Ala Ala Glu Ile Leu
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cgc gaa ggt ccg ccg ccg gaa gtg gtg gct cgt ttt acc gac aac att   915
Arg Glu Gly Pro Pro Pro Glu Val Val Ala Arg Phe Thr Asp Asn Ile
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ctg acg caa aat gcg cga atg cag gca ctg gtg gaa acg tta cta cgc   963
Leu Thr Gln Asn Ala Arg Met Gln Ala Leu Val Glu Thr Leu Leu Arg
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cag gca aga ctg gag aat cgt cag gaa gtc gtt ctg act gct gtt gat   1011
Gln Ala Arg Leu Glu Asn Arg Gln Glu Val Val Leu Thr Ala Val Asp
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Val Ala Ala Leu Phe Arg Arg Val Ser Glu Ala Arg Thr Val Gln Leu
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gca gaa aaa aac atc act ttg cat gtt atg cct act gag gtt aac gtt   1107
Ala Glu Lys Asn Ile Thr Leu His Val Met Pro Thr Glu Val Asn Val
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gct tct gaa ccg gcg tta ctg gag cag gcg ctg ggg aat tta ctg gat   1155
Ala Ser Glu Pro Ala Leu Leu Glu Gln Ala Leu Gly Asn Leu Leu Asp
            365                 370                 375

aac gcc atc gat ttt act ccc gag agc ggt tgc ata acg cta agc gcc   1203
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    395                 400                 405

ggg att cct gac tac gcg ctg tca cgt att ttt gaa cgc ttt tac tct   1299
Gly Ile Pro Asp Tyr Ala Leu Ser Arg Ile Phe Glu Arg Phe Tyr Ser
410                 415                 420                 425

ttg ccg cgt gca aat ggg caa aaa agc agc ggt ctg ggg ttg gcg ttt   1347
Leu Pro Arg Ala Asn Gly Gln Lys Ser Ser Gly Leu Gly Leu Ala Phe
                430                 435                 440

gtc agt gag gtc gcc cgt ttg ttt aac ggc gaa gtc acg ctg cgc aac   1395
Val Ser Glu Val Ala Arg Leu Phe Asn Gly Glu Val Thr Leu Arg Asn
            445                 450                 455

gtg cag gaa ggt ggc gtg ctg gcc tcg ctt cga ctt cac cgt cac ttc   1443
Val Gln Glu Gly Gly Val Leu Ala Ser Leu Arg Leu His Arg His Phe
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         35                  40                  45

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        195                 200                 205

Ser Ile Ala Arg Leu Thr Arg Tyr Ala Asp Ser Val Thr Asp Asn Lys
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Glu Gln Tyr Val Tyr Ala Leu Thr His Glu Leu Lys Ser Pro Leu Ala
            260                 265                 270

Ala Ile Arg Gly Ala Ala Glu Ile Leu Arg Glu Gly Pro Pro Pro Glu
        275                 280                 285

Val Val Ala Arg Phe Thr Asp Asn Ile Leu Thr Gln Asn Ala Arg Met
    290                 295                 300

Gln Ala Leu Val Glu Thr Leu Leu Arg Gln Ala Arg Leu Glu Asn Arg
305                 310                 315                 320

Gln Glu Val Val Leu Thr Ala Val Asp Val Ala Ala Leu Phe Arg Arg
                325                 330                 335
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```
Val Ser Glu Ala Arg Thr Val Gln Leu Ala Glu Lys Asn Ile Thr Leu
            340                 345                 350

His Val Met Pro Thr Glu Val Asn Val Ala Ser Glu Pro Ala Leu Leu
        355                 360                 365

Glu Gln Ala Leu Gly Asn Leu Leu Asp Asn Ala Ile Asp Phe Thr Pro
    370                 375                 380

Glu Ser Gly Cys Ile Thr Leu Ser Ala Glu Val Asp Gln Glu Tyr Val
385                 390                 395                 400

Thr Leu Lys Val Leu Asp Thr Gly Ser Gly Ile Pro Asp Tyr Ala Leu
                405                 410                 415

Ser Arg Ile Phe Glu Arg Phe Tyr Ser Leu Pro Arg Ala Asn Gly Gln
            420                 425                 430

Lys Ser Ser Gly Leu Gly Leu Ala Phe Val Ser Glu Val Ala Arg Leu
        435                 440                 445

Phe Asn Gly Glu Val Thr Leu Arg Asn Val Gln Glu Gly Gly Val Leu
    450                 455                 460

Ala Ser Leu Arg Leu His Arg His Phe Thr
465                 470
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<210> 6
<211> 128
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<213> Escherichia coli

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<221> CDS
<222> (1)..(126)

<400> 6

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atg aaa ggt cgc ctg tta gat gct gtc ccg ctc agt tcc cta acg ggc   48
Met Lys Gly Arg Leu Leu Asp Ala Val Pro Leu Ser Ser Leu Thr Gly
  1               5                  10                  15

gtt ggc gca gcg ctt agt aac aag ctg gcg aaa atc aac ctg cat acc   96
Val Gly Ala Ala Leu Ser Asn Lys Leu Ala Lys Ile Asn Leu His Thr
             20                  25                  30

gta cag gat tta ctc tta cac ctt cct ctg cg                       128
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Val Gln Asp Leu Leu Leu His Leu Pro Leu
35 40

<210> 7
<211> 42
<212> PRT
<213> Escherichia coli

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Met Lys Gly Arg Leu Leu Asp Ala Val Pro Leu Ser Ser Leu Thr Gly
1 5 10 15

Val Gly Ala Ala Leu Ser Asn Lys Leu Ala Lys Ile Asn Leu His Thr
20 25 30

Val Gln Asp Leu Leu Leu His Leu Pro Leu
35 40

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<211> 1174
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<213> Escherichia coli

<220>
<221> CDS
<222> (121)..(837)

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cactttgtta tcaatctggg gccagcaaat gctggcctga tttgttcttg agggaagact 120

atg atg cgc aaa atg ctg ctg gcg gca gca ctt tca gtg acg gca atg 168
Met Met Arg Lys Met Leu Leu Ala Ala Ala Leu Ser Val Thr Ala Met
1 5 10 15

acc gct cac gcc gac tac cag tgc agc gtc acg ccg cgt gac gat gtg 216
Thr Ala His Ala Asp Tyr Gln Cys Ser Val Thr Pro Arg Asp Asp Val
20 25 30

att gtc agc ccg caa acc gtg cag gtg aag ggc gaa aac ggc aat ctg 264
Ile Val Ser Pro Gln Thr Val Gln Val Lys Gly Glu Asn Gly Asn Leu
35 40 45

gtg atc acg cca gac ggc aac gtg atg tat aac ggt aag caa tat tcc 312

```
Val Ile Thr Pro Asp Gly Asn Val Met Tyr Asn Gly Lys Gln Tyr Ser
     50                  55                  60

ctg aat gcc gcc cag cgc gag cag gcg aag gat tat cag gct gaa cta   360
Leu Asn Ala Ala Gln Arg Glu Gln Ala Lys Asp Tyr Gln Ala Glu Leu
 65                  70                  75                  80

cgt agc acc ctg ccg tgg att gat gga ggc gcg aaa agc cgc gtc gag   408
Arg Ser Thr Leu Pro Trp Ile Asp Gly Gly Ala Lys Ser Arg Val Glu
                 85                  90                  95

aaa gct cgt att gcg ctg gat aaa att atc gtt cag gag atg ggc gaa   456
Lys Ala Arg Ile Ala Leu Asp Lys Ile Ile Val Gln Glu Met Gly Glu
            100                 105                 110

agc agc aaa atg cgc agc cgt ctg acc aaa ctt gat gcg cag ctg aaa   504
Ser Ser Lys Met Arg Ser Arg Leu Thr Lys Leu Asp Ala Gln Leu Lys
        115                 120                 125

gag cag atg aac cgc att atc gaa acg cgc agc gat ggc ctg acg ttt   552
Glu Gln Met Asn Arg Ile Ile Glu Thr Arg Ser Asp Gly Leu Thr Phe
    130                 135                 140

cac tat aaa gcc att gat cag gtt cgt gcc gaa ggc cag caa tta gtg   600
His Tyr Lys Ala Ile Asp Gln Val Arg Ala Glu Gly Gln Gln Leu Val
145                 150                 155                 160

aat cag gca atg ggc gga att tta cag gac agc att aat gaa atg ggc   648
Asn Gln Ala Met Gly Gly Ile Leu Gln Asp Ser Ile Asn Glu Met Gly
                165                 170                 175

gcg aaa gcg gtg ctg aaa agc ggc ggt aac cca tta cag aac gtg ctg   696
Ala Lys Ala Val Leu Lys Ser Gly Gly Asn Pro Leu Gln Asn Val Leu
            180                 185                 190

gga agc ctg ggc ggc ctg caa tcc tca atc caa acc gag tgg aaa aag   744
Gly Ser Leu Gly Gly Leu Gln Ser Ser Ile Gln Thr Glu Trp Lys Lys
        195                 200                 205

cag gaa aaa gat ttc cag cag ttt ggc aaa gat gtt tgt agc cgc gtt   792
Gln Glu Lys Asp Phe Gln Gln Phe Gly Lys Asp Val Cys Ser Arg Val
    210                 215                 220

gtg act ctg gaa gat agc cgc aaa gcc ctg gtc ggg aat tta aaa       837
Val Thr Leu Glu Asp Ser Arg Lys Ala Leu Val Gly Asn Leu Lys
225                 230                 235

taatcctcta ttttaagacg gcataatact tttttatgcc gtttaattct tcgttttgtt 897
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acctgcctct aactttgtaa gggcgaattc tgcagatatc catcacactg gcggccgctc 957

gagcatgcat ctagagggcc caattcgccc tatagtgagt cgtattacaa ttcactggcc 1017

gtcgttttac aaccgtcgtg actgggaaaa ccctggcgtt acccaactta atcgccttgc 1077

agcacatccc cctttcgcca gctggcgtaa tagcgaaaag gcccgcaccg atcgcccttc 1137

caacagttgc gcacctgatg gccaatggac gcgcctg 1174

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<211> 239
<212> PRT
<213> Escherichia coli

<400> 9

Met Met Arg Lys Met Leu Leu Ala Ala Ala Leu Ser Val Thr Ala Met
1 5 10 15

Thr Ala His Ala Asp Tyr Gln Cys Ser Val Thr Pro Arg Asp Asp Val
20 25 30

Ile Val Ser Pro Gln Thr Val Gln Val Lys Gly Glu Asn Gly Asn Leu
35 40 45

Val Ile Thr Pro Asp Gly Asn Val Met Tyr Asn Gly Lys Gln Tyr Ser
50 55 60

Leu Asn Ala Ala Gln Arg Glu Gln Ala Lys Asp Tyr Gln Ala Glu Leu
65 70 75 80

Arg Ser Thr Leu Pro Trp Ile Asp Gly Gly Ala Lys Ser Arg Val Glu
85 90 95

Lys Ala Arg Ile Ala Leu Asp Lys Ile Ile Val Gln Glu Met Gly Glu
100 105 110

Ser Ser Lys Met Arg Ser Arg Leu Thr Lys Leu Asp Ala Gln Leu Lys
115 120 125

Glu Gln Met Asn Arg Ile Ile Glu Thr Arg Ser Asp Gly Leu Thr Phe
130 135 140

His Tyr Lys Ala Ile Asp Gln Val Arg Ala Glu Gly Gln Gln Leu Val
145 150 155 160

Asn Gln Ala Met Gly Gly Ile Leu Gln Asp Ser Ile Asn Glu Met Gly
165 170 175

Ala Lys Ala Val Leu Lys Ser Gly Gly Asn Pro Leu Gln Asn Val Leu
180 185 190

Gly Ser Leu Gly Gly Leu Gln Ser Ser Ile Gln Thr Glu Trp Lys Lys
195 200 205

Gln Glu Lys Asp Phe Gln Gln Phe Gly Lys Asp Val Cys Ser Arg Val
210 215 220

Val Thr Leu Glu Asp Ser Arg Lys Ala Leu Val Gly Asn Leu Lys
225 230 235

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<210> 10
<211> 3406
<212> DNA
<213> Escherichia coli

<220>
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<222> (1007)..(1276)

<220>
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<222> (1280)..(1792)

<220>
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<222> (1798)..(2574)

<220>
<221> CDS
<222> (2604)..(3398)

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aaacggcacc aacatgaaat tgctggcgga acgcggcgtg caggtgttct tcactcaggt 120

ctttcgcgac agctttttcc atgctgatat gcaccctggc aacatcttcg taagctatga 180

acacccggaa aacccgaaat atatcggcat tgattgcggg attgttggct cgctaaacaa 240

agaagataaa cgctatctgg cggaaaactt tatcgccttc tttaatcgcg actatcgcaa 300

agtggcagag ctacacgtcg attctggttg ggtgccacca gataccaacg ttgaagagtt 360

cgaatttgcc attcgtacgg tctgtgaacc tatctttgag aaaccgctgg ccgaaatttc 420

gtttggacat gtactgttaa atctgtttaa tacggcgcgt cgcttcaata tggaagtgca 480

gccgcaactg gtgttactcc agaaaaccct gctctacgtc gaaggggtag gacgccagct 540

ttatccgcaa ctcgatttat ggaaaacggc gaagcctttc ctggagtcgt ggattaaaga 600

tcaggtcggt attcctgcgc tggtgagagc atttaaagaa aaagcgccgt tctgggtcga 660

aaaaatgcca gaactgcctg aactggttta cgacagtttg cgccagggca agtatttaca 720

gcatagtgtt ggtaagattg cccgcgagct tcagtcaaat catgtacgtc agggacaatt 780

cgcgttattt tctcggaatt ggcgctacgt tagtatttaa gtggcacatt cttgttggtc 840

agccgacctg aatgggggct gatgcccggc tggttaatgg caggtggtct gatcgcctgg 900

tttgtccggt tggcgcaaaa cacgctgatt ttttcatcgc tcaaggcggg ccgtgtaacg 960

tataatgcgg ctttgtttaa tcatcatcta ccacagagga acatgt atg ggt ggt 1015
Met Gly Gly
1

atc agt att tgg cag tta ttg att att gcc gtc atc gtt gta ctg ctt 1063
Ile Ser Ile Trp Gln Leu Leu Ile Ile Ala Val Ile Val Val Leu Leu
5 10 15

ttt ggc acc aaa aag ctc ggc tcc atc ggt tcc gat ctt ggt gcg tcg 1111
Phe Gly Thr Lys Lys Leu Gly Ser Ile Gly Ser Asp Leu Gly Ala Ser
20 25 30 35

atc aaa ggc ttt aaa aaa gca atg agc gat gat gaa cca aag cag gat 1159
Ile Lys Gly Phe Lys Lys Ala Met Ser Asp Asp Glu Pro Lys Gln Asp
40 45 50

aaa acc agc cag gat gct gat ttt act gcg aaa act atc gcc gat aag 1207
Lys Thr Ser Gln Asp Ala Asp Phe Thr Ala Lys Thr Ile Ala Asp Lys
55 60 65

cag gcg gat acg aat cag gaa cag gct aaa ata gaa gac gcg aag cgc 1255
Gln Ala Asp Thr Asn Gln Glu Gln Ala Lys Ile Glu Asp Ala Lys Arg
70 75 80

cac gat aaa gag cag gtg taa tct gtg ttt gat atc ggt ttt agc gaa 1303

```
His Asp Lys Glu Gln Val          Val Phe Asp Ile Gly Phe Ser Glu
 85                  90                  95

ctg cta ttg gtg ttc atc atc ggc ctc gtc gtt ctg ggg ccg caa cga  1351
Leu Leu Leu Val Phe Ile Ile Gly Leu Val Val Leu Gly Pro Gln Arg
100                 105                 110

ctg cct gtg gcg gta aaa acg gta gcg ggc tgg att cgc gcg ttg cgt  1399
Leu Pro Val Ala Val Lys Thr Val Ala Gly Trp Ile Arg Ala Leu Arg
115                 120                 125                 130

tca ctg gcg aca acg gtg cag aac gaa ctg acc cag gag tta aaa ctc  1447
Ser Leu Ala Thr Thr Val Gln Asn Glu Leu Thr Gln Glu Leu Lys Leu
                135                 140                 145

cag gag ttt cag gac agt ctg aaa aag gtt gaa aag gcg agc ctc act  1495
Gln Glu Phe Gln Asp Ser Leu Lys Lys Val Glu Lys Ala Ser Leu Thr
            150                 155                 160

aac ctg acg ccc gaa ctg aaa gcg tcg atg gat gaa tta cgc cag gct  1543
Asn Leu Thr Pro Glu Leu Lys Ala Ser Met Asp Glu Leu Arg Gln Ala
        165                 170                 175

gcg gag tcg atg aaa cgt tcc tac gtt gca aac gat cct gaa aag gcg  1591
Ala Glu Ser Met Lys Arg Ser Tyr Val Ala Asn Asp Pro Glu Lys Ala
    180                 185                 190

agc gat gaa gcg cac acc atc cat aac ccg gtg gtg aaa gac aat gaa  1639
Ser Asp Glu Ala His Thr Ile His Asn Pro Val Val Lys Asp Asn Glu
195                 200                 205                 210

act gcg cat gaa ggc gta acg cct gct gct gca caa acg cag gcc agt  1687
Thr Ala His Glu Gly Val Thr Pro Ala Ala Ala Gln Thr Gln Ala Ser
                215                 220                 225

tcg ccg gaa cag aag cca gaa acc acg cca gag ccg gtg gta aaa cct  1735
Ser Pro Glu Gln Lys Pro Glu Thr Thr Pro Glu Pro Val Val Lys Pro
            230                 235                 240

gct gcg gac gct gaa ccg aaa acc gct gca cct tcc cct tcg tcg agt  1783
Ala Ala Asp Ala Glu Pro Lys Thr Ala Ala Pro Ser Pro Ser Ser Ser
        245                 250                 255

gat aaa ccg taaac atg tct gta gaa gat act caa ccg ctt atc acg cat 1833
Asp Lys Pro       Met Ser Val Glu Asp Thr Gln Pro Leu Ile Thr His
    260                     265                 270

ctg att gag ctg cgt aag cgt ctg ctg aac tgc att atc tcg gtg atc  1881
```

```
Leu Ile Glu Leu Arg Lys Arg Leu Leu Asn Cys Ile Ile Ser Val Ile
    275                 280                 285

gtg ata ttc ctg tgt ctg gtc tat ttc gcc aat gac atc tat cac ctg   1929
Val Ile Phe Leu Cys Leu Val Tyr Phe Ala Asn Asp Ile Tyr His Leu
290                 295                 300                 305

gta tcc gcg cca ctg atc aag cag ttg ccg caa ggt tca acg atg atc   1977
Val Ser Ala Pro Leu Ile Lys Gln Leu Pro Gln Gly Ser Thr Met Ile
                310                 315                 320

gcc acc gac gtg gcc tcg ccg ttc ttt acg ccg atc aag ctg acc ttt   2025
Ala Thr Asp Val Ala Ser Pro Phe Phe Thr Pro Ile Lys Leu Thr Phe
            325                 330                 335

atg gtg tcg ctg att ctg tca gcg ccg gtg att ctc tat cag gtg tgg   2073
Met Val Ser Leu Ile Leu Ser Ala Pro Val Ile Leu Tyr Gln Val Trp
        340                 345                 350

gcg ttt atc gcc cca gcg ctg tat aag cat gaa cgt cgc ctg gtg gtg   2121
Ala Phe Ile Ala Pro Ala Leu Tyr Lys His Glu Arg Arg Leu Val Val
    355                 360                 365

ccg ctg ctg gtt tcc agc tct ctg ctg ttt tat atc ggc atg gcg ttc   2169
Pro Leu Leu Val Ser Ser Ser Leu Leu Phe Tyr Ile Gly Met Ala Phe
370                 375                 380                 385

gcc tac ttt gtg gtc ttt ccg ctg gca ttt ggc ttc ctt gcc aat acc   2217
Ala Tyr Phe Val Val Phe Pro Leu Ala Phe Gly Phe Leu Ala Asn Thr
                390                 395                 400

gcg ccg gaa ggg gta cag gta tcc acc gac atc gcg agc tat tta agc   2265
Ala Pro Glu Gly Val Gln Val Ser Thr Asp Ile Ala Ser Tyr Leu Ser
            405                 410                 415

ttc gtt atg gcg ctg ttt atg gcg ttt ggt gtc tcc ttt gaa gtg ccg   2313
Phe Val Met Ala Leu Phe Met Ala Phe Gly Val Ser Phe Glu Val Pro
        420                 425                 430

gtg gca att gtg ctg ctg tgc tgg atg ggg att acc tcg cca gaa gac   2361
Val Ala Ile Val Leu Leu Cys Trp Met Gly Ile Thr Ser Pro Glu Asp
    435                 440                 445

tta cgc aaa aaa cgc ccg tat gtg ctg gtt ggt gca ttc gtt gtc ggg   2409
Leu Arg Lys Lys Arg Pro Tyr Val Leu Val Gly Ala Phe Val Val Gly
450                 455                 460                 465

atg ttg ctg acg ccg ccg gat gtc ttc tcg caa acg ctg ttg gcg atc   2457
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```
Met Leu Leu Thr Pro Pro Asp Val Phe Ser Gln Thr Leu Leu Ala Ile
                470                 475                 480

cct atg tac tgc ctg ttt gaa atc ggt gtc ttc ttc tca cgc ttt tac   2505
Pro Met Tyr Cys Leu Phe Glu Ile Gly Val Phe Phe Ser Arg Phe Tyr
            485                 490                 495

gtt ggt aaa ggg cga aac cgg gaa gag gaa aac gac gct gaa gca gaa   2553
Val Gly Lys Gly Arg Asn Arg Glu Glu Glu Asn Asp Ala Glu Ala Glu
        500                 505                 510

agc gaa aaa act gaa gaa taa attcaaccgc ccgtcagggc ggttgtcat atg   2606
Ser Glu Lys Thr Glu Glu                                     Met
    515                 520

gag tac agg atg ttt gat atc ggc gtt aat ttg acc agt tcg caa ttt   2654
Glu Tyr Arg Met Phe Asp Ile Gly Val Asn Leu Thr Ser Ser Gln Phe
            525                 530                 535

gcg aaa gac cgt gat gat gtt gta gcg cgc gct ttt gac gcg gga gtt   2702
Ala Lys Asp Arg Asp Asp Val Val Ala Arg Ala Phe Asp Ala Gly Val
        540                 545                 550

aat ggg cta ctc atc acc ggt acc aat ctg cgt gaa agc cag cag gcg   2750
Asn Gly Leu Leu Ile Thr Gly Thr Asn Leu Arg Glu Ser Gln Gln Ala
    555                 560                 565

caa aag ctg gcg cgt cag tat tcg tcc tgt tgg tca acg gcg ggc gta   2798
Gln Lys Leu Ala Arg Gln Tyr Ser Ser Cys Trp Ser Thr Ala Gly Val
570                 575                 580                 585

cat cct cac gac agc agc cag tgg caa gct gtg act gaa gaa gcg att   2846
His Pro His Asp Ser Ser Gln Trp Gln Ala Val Thr Glu Glu Ala Ile
                590                 595                 600

att gag ctg gcc gcg cag cca gaa gtg gtg gcg att ggt gaa tgt ggt   2894
Ile Glu Leu Ala Ala Gln Pro Glu Val Val Ala Ile Gly Glu Cys Gly
            605                 610                 615

ctc gac ttt aac cgc aac ttt tcg acg ccg gaa gag cag gaa cgc gct   2942
Leu Asp Phe Asn Arg Asn Phe Ser Thr Pro Glu Glu Gln Glu Arg Ala
        620                 625                 630

ttt gtt gcc cag cta cgc att gcc gca gaa tta aac atg ccg gta ttt   2990
Phe Val Ala Gln Leu Arg Ile Ala Ala Glu Leu Asn Met Pro Val Phe
    635                 640                 645

atg cac tgt cgc gat gcc cac gag cgg ttt atg aca ttg ctg gag ccg   3038
```

```
Met His Cys Arg Asp Ala His Glu Arg Phe Met Thr Leu Leu Glu Pro
650                 655                 660                 665

tgg ctg gat aaa ctg cct ggt gcg gtt ctt cat tgc ttt acc ggc aca   3086
Trp Leu Asp Lys Leu Pro Gly Ala Val Leu His Cys Phe Thr Gly Thr
                670                 675                 680

cgc gaa gag atg cag gcg tgc gtg gcg tgt gga att tat atc ggc att   3134
Arg Glu Glu Met Gln Ala Cys Val Ala Cys Gly Ile Tyr Ile Gly Ile
            685                 690                 695

acc ggt tgg gtt tgc gat gaa cga cgc ggg ctg gag ctg cgg gaa ttg   3182
Thr Gly Trp Val Cys Asp Glu Arg Arg Gly Leu Glu Leu Arg Glu Leu
        700                 705                 710

ttg ccg ttg att ccg gcg gag aaa ttg ctg atc gaa act gat gcg ccg   3230
Leu Pro Leu Ile Pro Ala Glu Lys Leu Leu Ile Glu Thr Asp Ala Pro
    715                 720                 725

tat ctg ctc cct cgc gat ctc acg cca aag cca tca tcc cgg cgc aac   3278
Tyr Leu Leu Pro Arg Asp Leu Thr Pro Lys Pro Ser Ser Arg Arg Asn
730                 735                 740                 745

gag cca gcc cat ctg ccc cat att ttg caa cgt att gcg cac tgg cgt   3326
Glu Pro Ala His Leu Pro His Ile Leu Gln Arg Ile Ala His Trp Arg
                750                 755                 760

gga gaa gat gcc gca tgg ctg gct gcc acc acg gat gcc aat gtc aaa   3374
Gly Glu Asp Ala Ala Trp Leu Ala Ala Thr Thr Asp Ala Asn Val Lys
            765                 770                 775

aca ctg ttt ggg att gcg ttt tag agtttgcg                         3406
Thr Leu Phe Gly Ile Ala Phe
        780                 785
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<210> 11
<211> 89
<212> PRT
<213> Escherichia coli

<400> 11

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Met Gly Gly Ile Ser Ile Trp Gln Leu Leu Ile Ile Ala Val Ile Val
  1               5                  10                  15

Val Leu Leu Phe Gly Thr Lys Lys Leu Gly Ser Ile Gly Ser Asp Leu
             20                  25                  30
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Gly Ala Ser Ile Lys Gly Phe Lys Lys Ala Met Ser Asp Asp Glu Pro
35 40 45

Lys Gln Asp Lys Thr Ser Gln Asp Ala Asp Phe Thr Ala Lys Thr Ile
50 55 60

Ala Asp Lys Gln Ala Asp Thr Asn Gln Glu Gln Ala Lys Ile Glu Asp
65 70 75 80

Ala Lys Arg His Asp Lys Glu Gln Val
85

<210> 12
<211> 171
<212> PRT
<213> Escherichia coli

<400> 12
Val Phe Asp Ile Gly Phe Ser Glu Leu Leu Leu Val Phe Ile Ile Gly
1 5 10 15

Leu Val Val Leu Gly Pro Gln Arg Leu Pro Val Ala Val Lys Thr Val
20 25 30

Ala Gly Trp Ile Arg Ala Leu Arg Ser Leu Ala Thr Thr Val Gln Asn
35 40 45

Glu Leu Thr Gln Glu Leu Lys Leu Gln Glu Phe Gln Asp Ser Leu Lys
50 55 60

Lys Val Glu Lys Ala Ser Leu Thr Asn Leu Thr Pro Glu Leu Lys Ala
65 70 75 80

Ser Met Asp Glu Leu Arg Gln Ala Ala Glu Ser Met Lys Arg Ser Tyr
85 90 95

Val Ala Asn Asp Pro Glu Lys Ala Ser Asp Glu Ala His Thr Ile His
100 105 110

Asn Pro Val Val Lys Asp Asn Glu Thr Ala His Glu Gly Val Thr Pro
115 120 125

Ala Ala Ala Gln Thr Gln Ala Ser Ser Pro Glu Gln Lys Pro Glu Thr
130 135 140

Thr Pro Glu Pro Val Val Lys Pro Ala Ala Asp Ala Glu Pro Lys Thr
145 150 155 160

Ala Ala Pro Ser Pro Ser Ser Ser Asp Lys Pro
165 170

<210> 13
<211> 258
<212> PRT
<213> Escherichia coli

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Met Ser Val Glu Asp Thr Gln Pro Leu Ile Thr His Leu Ile Glu Leu
1 5 10 15

Arg Lys Arg Leu Leu Asn Cys Ile Ile Ser Val Ile Val Ile Phe Leu
20 25 30

Cys Leu Val Tyr Phe Ala Asn Asp Ile Tyr His Leu Val Ser Ala Pro
35 40 45

Leu Ile Lys Gln Leu Pro Gln Gly Ser Thr Met Ile Ala Thr Asp Val
50 55 60

Ala Ser Pro Phe Phe Thr Pro Ile Lys Leu Thr Phe Met Val Ser Leu
65 70 75 80

Ile Leu Ser Ala Pro Val Ile Leu Tyr Gln Val Trp Ala Phe Ile Ala
85 90 95

Pro Ala Leu Tyr Lys His Glu Arg Arg Leu Val Val Pro Leu Leu Val
100 105 110

Ser Ser Ser Leu Leu Phe Tyr Ile Gly Met Ala Phe Ala Tyr Phe Val
115 120 125

Val Phe Pro Leu Ala Phe Gly Phe Leu Ala Asn Thr Ala Pro Glu Gly
130 135 140

Val Gln Val Ser Thr Asp Ile Ala Ser Tyr Leu Ser Phe Val Met Ala
145 150 155 160

Leu Phe Met Ala Phe Gly Val Ser Phe Glu Val Pro Val Ala Ile Val
165 170 175

Leu Leu Cys Trp Met Gly Ile Thr Ser Pro Glu Asp Leu Arg Lys Lys
180 185 190

Arg Pro Tyr Val Leu Val Gly Ala Phe Val Val Gly Met Leu Leu Thr

195 200 205

Pro Pro Asp Val Phe Ser Gln Thr Leu Leu Ala Ile Pro Met Tyr Cys
210 215 220

Leu Phe Glu Ile Gly Val Phe Phe Ser Arg Phe Tyr Val Gly Lys Gly
225 230 235 240

Arg Asn Arg Glu Glu Glu Asn Asp Ala Glu Ala Glu Ser Glu Lys Thr
245 250 255

Glu Glu

<210> 14
<211> 264
<212> PRT
<213> Escherichia coli

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Met Glu Tyr Arg Met Phe Asp Ile Gly Val Asn Leu Thr Ser Ser Gln
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Phe Ala Lys Asp Arg Asp Asp Val Val Ala Arg Ala Phe Asp Ala Gly
20 25 30

Val Asn Gly Leu Leu Ile Thr Gly Thr Asn Leu Arg Glu Ser Gln Gln
35 40 45

Ala Gln Lys Leu Ala Arg Gln Tyr Ser Ser Cys Trp Ser Thr Ala Gly
50 55 60

Val His Pro His Asp Ser Ser Gln Trp Gln Ala Val Thr Glu Glu Ala
65 70 75 80

Ile Ile Glu Leu Ala Ala Gln Pro Glu Val Val Ala Ile Gly Glu Cys
85 90 95

Gly Leu Asp Phe Asn Arg Asn Phe Ser Thr Pro Glu Glu Gln Glu Arg
100 105 110

Ala Phe Val Ala Gln Leu Arg Ile Ala Ala Glu Leu Asn Met Pro Val
115 120 125

Phe Met His Cys Arg Asp Ala His Glu Arg Phe Met Thr Leu Leu Glu
130 135 140

Pro Trp Leu Asp Lys Leu Pro Gly Ala Val Leu His Cys Phe Thr Gly

145 150 155 160

Thr Arg Glu Glu Met Gln Ala Cys Val Ala Cys Gly Ile Tyr Ile Gly
165 170 175

Ile Thr Gly Trp Val Cys Asp Glu Arg Arg Gly Leu Glu Leu Arg Glu
180 185 190

Leu Leu Pro Leu Ile Pro Ala Glu Lys Leu Leu Ile Glu Thr Asp Ala
195 200 205

Pro Tyr Leu Leu Pro Arg Asp Leu Thr Pro Lys Pro Ser Ser Arg Arg
210 215 220

Asn Glu Pro Ala His Leu Pro His Ile Leu Gln Arg Ile Ala His Trp
225 230 235 240

Arg Gly Glu Asp Ala Ala Trp Leu Ala Ala Thr Thr Asp Ala Asn Val
245 250 255

Lys Thr Leu Phe Gly Ile Ala Phe
260

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<210> 15
<211> 586
<212> DNA
<213> Escherichia coli

<220>
<221> CDS
<222> (170)..(370)

<400> 15
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tgattcacct tgttacagat tgctattgtg tgcgcgcgtc gaatgaccgt taatattctc 120

tggtttttaa ggcgcgttct gttgccggtt atatgtcaag aaggtatct atg ggt gag 178
Met Gly Glu
1

att agt att acc aaa ctg ctg gta gtt gcg gcg ctg gtc gtt ctg ctg 226
Ile Ser Ile Thr Lys Leu Leu Val Val Ala Ala Leu Val Val Leu Leu
5 10 15

ttt ggg act aag aag tta cgt acg ctg ggc gga gac ctt gga gcg gcc 274

Phe Gly Thr Lys Lys Leu Arg Thr Leu Gly Gly Asp Leu Gly Ala Ala
20 25 30 35

att aaa ggg ttc aag aag gcg atg aat gat gac gat gct gcg gcg aaa 322
Ile Lys Gly Phe Lys Lys Ala Met Asn Asp Asp Asp Ala Ala Ala Lys
40 45 50

aaa ggc gca gac gtt gat ctt cag gct gaa aag ctc tct cat aaa gag 370
Lys Gly Ala Asp Val Asp Leu Gln Ala Glu Lys Leu Ser His Lys Glu
55 60 65

tgacgtggcg agcaggacgc tccctcaata tcttgttcga tacaaaaacc cgcttcaaaa 430

agcgggtttt ttatcagaca gatgtaagta attattacag gattacttaa cttccatccc 490

tttcgcctgc aaatcggcgt ggtaagaaga gcggacaaac ggaccgcatg cagcatgggt 550

aaagcccatc gccagcgctt cgctttcatt tcgtcg 586

<210> 16
<211> 67
<212> PRT
<213> Escherichia coli

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Met Gly Glu Ile Ser Ile Thr Lys Leu Leu Val Val Ala Ala Leu Val
1 5 10 15

Val Leu Leu Phe Gly Thr Lys Lys Leu Arg Thr Leu Gly Gly Asp Leu
20 25 30

Gly Ala Ala Ile Lys Gly Phe Lys Lys Ala Met Asn Asp Asp Asp Ala
35 40 45

Ala Ala Lys Lys Gly Ala Asp Val Asp Leu Gln Ala Glu Lys Leu Ser
50 55 60

His Lys Glu
65

<210> 17
<211> 4200
<212> DNA
<213> Salmonella typhimurium

<220>
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<222> (947)..(1444)

<220>
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<222> (1450)..(1722)

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atcacagagg aacatgtatg ggtggtatca gtatttggca gttgttgatt gttgccgtta 180

tcgtcgtact gctgttcggc accaaaaaac tcggttccat cggttccgat cttggcgcgt 240

ctatcaaagg ctttaaaaag gccatgagcg atgatgatgc caaacaggat aaaaccagtc 300

aggacgctga ttttaccgct aaatctatcg cggataagca aggcgaagcg aaaaaggaag 360

acgctaaaag ccaagataaa gagcaggtat aatccgtgtt tgatatcggt tttagcgaac 420

tgctgttagt gttcgttatc ggcctcattg tgttggggcc gcaacgattg ccagtagcgg 480

taaaaacggt agcgggctgg attcgcgcgt tgcggtccct tgcgacaacg gttcagaatg 540

aactgactca ggaactgaaa cttcaggagt tccaggacag tctgaaaaaa gtcgaaaagg 600

cgagcctgga aaatctgact cccgaactga aagcatctat ggatgaactg cgtcaggcgg 660

cggagtcgat gaaacgcacc tacagcgcta acgatcccga acaagcgagc gatgaagcgc 720

ataccatcca taatccggtg gtaaaaggga acgaaacgca gcatgagggc gtcacccctg 780

ccgccgctga aacacaggcg agcgcgccgg aacaaaagcc ggagcccgtt aaagctaacg 840

tgcctgagtc gacggaaacc gcttccgtag ccacgataga cgccgagaag aaatccgctg 900

cgcctgttgt cgaatcttcc ccctcgtcga gtgataaacc gtaaac atg gct gta 955
Met Ala Val
1

gaa gat act caa ccg ctt atc acg cat ctg atc gag ttg cgt aag cgc 1003
Glu Asp Thr Gln Pro Leu Ile Thr His Leu Ile Glu Leu Arg Lys Arg
5 10 15

ctg cta aac tgc atc gtc gca gta ctt ctg att ttt ctg gcg tta att 1051

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Leu Leu Asn Cys Ile Val Ala Val Leu Leu Ile Phe Leu Ala Leu Ile
 20                  25                  30                  35

tat ttc gcc aat gat att tat cat tta gtc gcc gca ccg ctg att aaa   1099
Tyr Phe Ala Asn Asp Ile Tyr His Leu Val Ala Ala Pro Leu Ile Lys
                 40                  45                  50

cag atg ccg caa ggg gcg aca atg att gcg acg gat gtg gcg tcg ccg   1147
Gln Met Pro Gln Gly Ala Thr Met Ile Ala Thr Asp Val Ala Ser Pro
             55                  60                  65

ttt ttt acg cct atc aaa ctc acc ttc atg gtg tct ttg atc tta tcc   1195
Phe Phe Thr Pro Ile Lys Leu Thr Phe Met Val Ser Leu Ile Leu Ser
         70                  75                  80

gcg cct gtc att ttg tac cag gtt tgg gcc ttt atc gcc ccg gcg ctg   1243
Ala Pro Val Ile Leu Tyr Gln Val Trp Ala Phe Ile Ala Pro Ala Leu
     85                  90                  95

tat aag cat gag cgt cgt ctg gtc gta cct ctg ctg gta tcc agc tcg   1291
Tyr Lys His Glu Arg Arg Leu Val Val Pro Leu Leu Val Ser Ser Ser
100                 105                 110                 115

ctg ctt ttc tat att ggt atg gcc ttc gcc tat ttt gtc gta ttc cct   1339
Leu Leu Phe Tyr Ile Gly Met Ala Phe Ala Tyr Phe Val Val Phe Pro
                120                 125                 130

ttg gcc ttt ggt ttc ctg acg cat acg gcg ccg gaa ggg gta cag gtt   1387
Leu Ala Phe Gly Phe Leu Thr His Thr Ala Pro Glu Gly Val Gln Val
            135                 140                 145

tcg aca gat atc gcc agc tat ctt agc ttt gtc atg gcg ctt ttt atg   1435
Ser Thr Asp Ile Ala Ser Tyr Leu Ser Phe Val Met Ala Leu Phe Met
        150                 155                 160

gcc ttt gcg tagcc ttt gaa gtg ccg gtg gcg att gtg ttg ctg tgc tgg 1485
Ala Phe Ala       Phe Glu Val Pro Val Ala Ile Val Leu Leu Cys Trp
    165                         170                 175

atg ggc atc acc acg cca gaa gat ttg cgt aaa aaa cgg cct tat atc   1533
Met Gly Ile Thr Thr Pro Glu Asp Leu Arg Lys Lys Arg Pro Tyr Ile
    180                 185                 190

ctg gtc ggg gca ttc att gtg gga atg ctg ctt acg ccg cca gat gtt   1581
Leu Val Gly Ala Phe Ile Val Gly Met Leu Leu Thr Pro Pro Asp Val
195                 200                 205                 210

ttc tcg caa acg ttg ctg gcg ata ccg atg tac tgc ctg ttt gaa att   1629
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Phe Ser Gln Thr Leu Leu Ala Ile Pro Met Tyr Cys Leu Phe Glu Ile
215 220 225

ggc gtt ttc tgc tca cgc ttt tat gtc ggt aag cga cgg acg cgc gac 1677
Gly Val Phe Cys Ser Arg Phe Tyr Val Gly Lys Arg Arg Thr Arg Asp
230 235 240

gaa gat aac gag gcc gaa acc gaa aag gcc gag cac act gaa gac 1722
Glu Asp Asn Glu Ala Glu Thr Glu Lys Ala Glu His Thr Glu Asp
245 250 255

taaacacaac cgcccgccag ggcggttgtc atatgggggc aagcatgttt gatattggcg 1782

ttaatttaac cagtagccag tttgcaaaag atcgtgatga tgtggtcgcc cgtgcgtttg 1842

cggcgggagt aaaaggtatg ctactgaccg gaacgaacat ccatgaaagt cagcaggcgt 1902

taaaactggc gcggcgctac ccccattgtt ggtcgacggc tggcgtccat ccccatgaca 1962

gcagtcagtg gtcacccgcg tctgaagacg ccattattgc gctggcgaac cagccggaag 2022

tcgtcgctat cggtgagtgc gggctggatt tcaatcgcaa tttttccacg ccgcaggagc 2082

aggagcgtgc ctttcaggcg cagctacaaa ttgccgccga attgcagata ccaatcttta 2142

tgcactgccg ggacgcgcat gagcgatttc tggtattgct tgatccctgg ctggatagtc 2202

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ggatcaaatt caacgaacag ataattagga aagagcggtt cgctgacgga ggtacgtttt 2922

ccgcgtacca ttttttccag ggtgatcatc ggtgtcaggc aacttaccgc ttgtctttcg 2982

aggtgttcct gagcacgctg aagttgcccg cgtttgcagt acagtaaata ccaggattgc 3042

ataatgactc ttatccgctt gttcggggcg caagcatagc aaaagccatg cgcgaagtta 3102

attatacact tcatccttta agccgtatct ggattagcgt tggttgccag agttcacgct 3162

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cgccatgccg gtgctgtgca acctttttgg cacgccaaaa cgcgtggcga tgggcatggg 3462

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ttctacgatc tggagtgctg cagcgcgaga tatcttgaag tacatgagcg gagagatgcg 4062

cggagacgta tgcgatcata cggcatatat gagtgatagc tcgtcttacg tcacgcaata 4122

acagcgtaga tgcatctata tcactatacg cgcgcatgag ctcgtatagg tgcctcatat 4182

ctcgtctatc tcaaagtc 4200

<210> 18
<211> 166
<212> PRT
<213> Salmonella typhimurium

<400> 18
Met Ala Val Glu Asp Thr Gln Pro Leu Ile Thr His Leu Ile Glu Leu
1 5 10 15

Arg Lys Arg Leu Leu Asn Cys Ile Val Ala Val Leu Leu Ile Phe Leu
20 25 30

Ala Leu Ile Tyr Phe Ala Asn Asp Ile Tyr His Leu Val Ala Ala Pro
35 40 45

Leu Ile Lys Gln Met Pro Gln Gly Ala Thr Met Ile Ala Thr Asp Val
50 55 60

Ala Ser Pro Phe Phe Thr Pro Ile Lys Leu Thr Phe Met Val Ser Leu
65 70 75 80

Ile Leu Ser Ala Pro Val Ile Leu Tyr Gln Val Trp Ala Phe Ile Ala
85 90 95

Pro Ala Leu Tyr Lys His Glu Arg Arg Leu Val Val Pro Leu Leu Val
100 105 110

Ser Ser Ser Leu Leu Phe Tyr Ile Gly Met Ala Phe Ala Tyr Phe Val
115 120 125

Val Phe Pro Leu Ala Phe Gly Phe Leu Thr His Thr Ala Pro Glu Gly
130 135 140

Val Gln Val Ser Thr Asp Ile Ala Ser Tyr Leu Ser Phe Val Met Ala
145 150 155 160

Leu Phe Met Ala Phe Ala
165

<210> 19
<211> 91
<212> PRT
<213> Salmonella typhimurium

<400> 19
Phe Glu Val Pro Val Ala Ile Val Leu Leu Cys Trp Met Gly Ile Thr
1 5 10 15

Thr Pro Glu Asp Leu Arg Lys Lys Arg Pro Tyr Ile Leu Val Gly Ala
20 25 30

Phe Ile Val Gly Met Leu Leu Thr Pro Pro Asp Val Phe Ser Gln Thr
35 40 45

Leu Leu Ala Ile Pro Met Tyr Cys Leu Phe Glu Ile Gly Val Phe Cys
50 55 60

Ser Arg Phe Tyr Val Gly Lys Arg Arg Thr Arg Asp Glu Asp Asn Glu
65 70 75 80

Ala Glu Thr Glu Lys Ala Glu His Thr Glu Asp
85 90

<210> 20
<211> 2601
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1572)..(2339)

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caaaaacccg tcccacctgg tttacgaagt tgccgactta tggtttcaca ccatgattct 120

tctgacacac cacgacctga aggcggaaga cgtattggac gaacttgcgc gccgccaagg 180

tttgtcgggc ttggccgaaa aagccgctcg cacagaatct tgaatttata ttaaaatccg 240

cactttccca cattcaatcc gtctgaccgc tgttcagacg gcatcggagc cgttatggac 300

aactgtattt tctgcaaaat cgccgccaaa gacattccgg cgcaaaccgt ctatgaagac 360

ggcgaaatgg tttgtttcaa agacatcaac cccgctgctc cggttcatct gctgctgatt 420

cccaaagtcc atttcgattc gttggcacac gccgcgcccg aacatcagcc ccttttggga 480

aaaatgatgc tgaaagttcc cgaaatcgcc aaagcggcag gactggcaga cggcttcaaa 540

accctgatca acaccggaaa aggcggcgga caagaggtct tccacctgca tatacacatc 600

atgggcacac ccgtataaac cgttatttca caatcaaccc ctaatactta cttaaggata 660

catcatgggc agtttttctc tgacgcactg gattatcgta ctgattatcg tcgttttgat 720

attcggcacc aaaaaactgc gcaacgtcgg caaagacctc ggcggtgcgg ttcatgactt 780

caaacagggg ctgaacgaag gtacagacgg caaagaagcc caaaaagacg atgtaatcga 840

acacaaaaaa gacgaagaca aagcgtaatt tatgtttgat ttcggtttgg gcgagctggt 900

ttttgtcggc attatcgccc tgattgtcct cggccccgaa cgcctgcccg aggccgcccg 960

caccgccgga cggctcatcg gcaggctgca acgctttgtc ggcagcgtca aacaggaatt 1020

tgacacgcaa atcgaactgg aagaactaag gaaggcaaag caggaatttg aagctgccgc 1080

tgctcaggtt cgagacagcc tcaaagaaac cggtacggat atggagggta atctgcacga 1140

catttccgac ggtctgaagc cttgggaaaa actgcccgaa cagcgcacgc ctgctgattt 1200

cggtgtcgat gaaaacggca atccctttcc cgatgcggca aacaccctat tagacggcat 1260

ttccgacgtt atgccgtccg aacgttccta cgcttccgcc gaaacccttg gggacagcgg 1320

gcaaaccggc agtacagccg aacccgcgga aaccgaccaa gaccgtgcat ggcgggaata 1380

cctgactgct tctgccgccg cacccgtcgt acagaccgtc gaagtcagct atatcgatac 1440

cgctgttgaa acccctgttc cgcataccac ttcgctgcgt aaacaggcaa taagccgcaa 1500

acgcgatttg cgtcctaaat cccgcgccaa acctaaattg cgcgtccgta aatcataaag 1560

agggcaatcc g gtg tcc gaa aca caa aac gaa caa ccc gtc caa ccg ctt 1610
Val Ser Glu Thr Gln Asn Glu Gln Pro Val Gln Pro Leu
1 5 10

gtc gag cat ctc atc gag ctg cgc cgc cgc ctg atg tgg acg gtt gtc 1658
Val Glu His Leu Ile Glu Leu Arg Arg Arg Leu Met Trp Thr Val Val
15 20 25

ggt atc tta gtc tgc ttt ttc ggc cta atg ccg ttt gcc caa caa ctc 1706
Gly Ile Leu Val Cys Phe Phe Gly Leu Met Pro Phe Ala Gln Gln Leu
30 35 40 45

tat act ttt atc gcc gac ccg ctg atg gca aac ctg ccc aaa gac acc 1754
Tyr Thr Phe Ile Ala Asp Pro Leu Met Ala Asn Leu Pro Lys Asp Thr
50 55 60

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agc atg att gcc acc gat gtc atc gca cca ttt ttc gtg ccg gtc aaa   1802
Ser Met Ile Ala Thr Asp Val Ile Ala Pro Phe Phe Val Pro Val Lys
            65                  70                  75

gtt acc ctg atg gcg gca ttt tta att tcg ctg ccg cat acg ctc tac   1850
Val Thr Leu Met Ala Ala Phe Leu Ile Ser Leu Pro His Thr Leu Tyr
        80                  85                  90

caa atc tgg gca ttc gtc gcc ccc gca ctc tac caa aac gaa aaa cgc   1898
Gln Ile Trp Ala Phe Val Ala Pro Ala Leu Tyr Gln Asn Glu Lys Arg
    95                  100                 105

ctg att acg ccg ctc gtc ctc tcc agc gtc agc ctg ttt ttc atc ggc   1946
Leu Ile Thr Pro Leu Val Leu Ser Ser Val Ser Leu Phe Phe Ile Gly
110                 115                 120                 125

atg gca ttt gcc tac ttt ttg gtt ttc ccc gtc att ttc aaa ttc ctt   1994
Met Ala Phe Ala Tyr Phe Leu Val Phe Pro Val Ile Phe Lys Phe Leu
                130                 135                 140

gcc agc gtt acc cct gtc ggt gtc aat atg gcg aca gac atc gac aaa   2042
Ala Ser Val Thr Pro Val Gly Val Asn Met Ala Thr Asp Ile Asp Lys
            145                 150                 155

tac ctc tcc ttc atc ttg ggg atg ttt gtc gca ttc ggt aca acg ttt   2090
Tyr Leu Ser Phe Ile Leu Gly Met Phe Val Ala Phe Gly Thr Thr Phe
        160                 165                 170

gaa gtc ccc att gtc gtt atc ctg tta acc aaa att ggt gtg gta aca   2138
Glu Val Pro Ile Val Val Ile Leu Leu Thr Lys Ile Gly Val Val Thr
    175                 180                 185

acc gaa cag ctc aaa cgc gcc cgc ccc tat gtg att gtc ggc gcg ttt   2186
Thr Glu Gln Leu Lys Arg Ala Arg Pro Tyr Val Ile Val Gly Ala Phe
190                 195                 200                 205

gtc att gcc gcc atc atc acg ccg ccc gat gtg att tca caa acc ctg   2234
Val Ile Ala Ala Ile Ile Thr Pro Pro Asp Val Ile Ser Gln Thr Leu
                210                 215                 220

ctt gcc att ccg ctg att ctc tta tac gaa gca ggt att tgg ttc gga   2282
Leu Ala Ile Pro Leu Ile Leu Leu Tyr Glu Ala Gly Ile Trp Phe Gly
            225                 230                 235

cgc ttt ttc acg cca cgt tca gaa cag gat ggc gac ata cag ccg cct   2330
Arg Phe Phe Thr Pro Arg Ser Glu Gln Asp Gly Asp Ile Gln Pro Pro
        240                 245                 250
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gca aca acc tgacactatg ccgtccgaac ctccgcctca taccgccaca 2379
Ala Thr Thr
255

gattaaggaa tacctttgaa taccctctat ttaggttcaa acagcccgcg ccgaatggaa 2439

atcctgacac agttgggcta tcaggtcgtc aagctgcctg ccaacatcga cgaaacggtc 2499

agacagaacg aagaccctgc ccgttacgtt caaaggatgg cagaagaaaa aaaccgaacc 2559

gccctgaccc tcttttgcga aaccaacggc acaatgcccg at 2601

<210> 21
<211> 256
<212> PRT
<213> Neisseria meningitidis

<400> 21
Val Ser Glu Thr Gln Asn Glu Gln Pro Val Gln Pro Leu Val Glu His
1 5 10 15

Leu Ile Glu Leu Arg Arg Arg Leu Met Trp Thr Val Val Gly Ile Leu
20 25 30

Val Cys Phe Phe Gly Leu Met Pro Phe Ala Gln Gln Leu Tyr Thr Phe
35 40 45

Ile Ala Asp Pro Leu Met Ala Asn Leu Pro Lys Asp Thr Ser Met Ile
50 55 60

Ala Thr Asp Val Ile Ala Pro Phe Phe Val Pro Val Lys Val Thr Leu
65 70 75 80

Met Ala Ala Phe Leu Ile Ser Leu Pro His Thr Leu Tyr Gln Ile Trp
85 90 95

Ala Phe Val Ala Pro Ala Leu Tyr Gln Asn Glu Lys Arg Leu Ile Thr
100 105 110

Pro Leu Val Leu Ser Ser Val Ser Leu Phe Phe Ile Gly Met Ala Phe
115 120 125

Ala Tyr Phe Leu Val Phe Pro Val Ile Phe Lys Phe Leu Ala Ser Val
130 135 140

Thr Pro Val Gly Val Asn Met Ala Thr Asp Ile Asp Lys Tyr Leu Ser
145 150 155 160

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Phe Ile Leu Gly Met Phe Val Ala Phe Gly Thr Thr Phe Glu Val Pro
                165                 170                 175

Ile Val Val Ile Leu Leu Thr Lys Ile Gly Val Val Thr Thr Glu Gln
            180                 185                 190

Leu Lys Arg Ala Arg Pro Tyr Val Ile Val Gly Ala Phe Val Ile Ala
        195                 200                 205

Ala Ile Ile Thr Pro Pro Asp Val Ile Ser Gln Thr Leu Leu Ala Ile
    210                 215                 220

Pro Leu Ile Leu Leu Tyr Glu Ala Gly Ile Trp Phe Gly Arg Phe Phe
225                 230                 235                 240

Thr Pro Arg Ser Glu Gln Asp Gly Asp Ile Gln Pro Pro Ala Thr Thr
                245                 250                 255
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<210> 22
<211> 4604
<212> DNA
<213> Escherichia coli

<220>
<221> CDS
<222> (2982)..(4082)

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<221> CDS
<222> (1534)..(2637)

<220>
<221> CDS
<222> (749)..(1531)

<220>
<221> CDS
<222> (6)..(746)

<400> 22

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      Val Asp Asp Asn Leu Lys Gly Gln Gly Ala Gly Lys Asn Phe Leu
        1               5                  10                  15

tcg ctg ata aag tac agc gag aca gat tat aca att tat tgt gac caa   98
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Ser Leu Ile Lys Tyr Ser Glu Thr Asp Tyr Thr Ile Tyr Cys Asp Gln
                 20                  25                  30

gat gat att tgg tta gaa aac aaa ata ttt gaa tta gta aag tat gca   146
Asp Asp Ile Trp Leu Glu Asn Lys Ile Phe Glu Leu Val Lys Tyr Ala
             35                  40                  45

aat gaa att aaa ttg aat gta tca gat gcg cct tcg cta gtt tat gct   194
Asn Glu Ile Lys Leu Asn Val Ser Asp Ala Pro Ser Leu Val Tyr Ala
         50                  55                  60

gat ggc tat gct tat atg gat ggt gag ggt aca atc gat ttt tct ggg   242
Asp Gly Tyr Ala Tyr Met Asp Gly Glu Gly Thr Ile Asp Phe Ser Gly
     65                  70                  75

ata tct aac aat cat gct gat caa tta aag gat ttt ctt ttt ttt aat   290
Ile Ser Asn Asn His Ala Asp Gln Leu Lys Asp Phe Leu Phe Phe Asn
 80                  85                  90                  95

ggt gga tac caa gga tgt tct att atg ttc aat cgt gca atg acc aaa   338
Gly Gly Tyr Gln Gly Cys Ser Ile Met Phe Asn Arg Ala Met Thr Lys
                100                 105                 110

ttt ctt ctg aat tat cga gga ttt gta tat cta cat gac gat atc aca   386
Phe Leu Leu Asn Tyr Arg Gly Phe Val Tyr Leu His Asp Asp Ile Thr
            115                 120                 125

aca tta gct gca tac gct ctt ggt aaa gtt tat ttt ctc ccg aaa tac   434
Thr Leu Ala Ala Tyr Ala Leu Gly Lys Val Tyr Phe Leu Pro Lys Tyr
        130                 135                 140

ctt atg tta tat aga cag cac acg aat gcg gta act ggt atc aaa aca   482
Leu Met Leu Tyr Arg Gln His Thr Asn Ala Val Thr Gly Ile Lys Thr
    145                 150                 155

ttc cgc aat gga ttg act tct aaa ttt aaa tca cca gta aac tat ctt   530
Phe Arg Asn Gly Leu Thr Ser Lys Phe Lys Ser Pro Val Asn Tyr Leu
160                 165                 170                 175

tta tca cga aaa cat tat cag gta aaa aaa tct ttt ttt gaa tgt aac   578
Leu Ser Arg Lys His Tyr Gln Val Lys Lys Ser Phe Phe Glu Cys Asn
                180                 185                 190

agc tct atc tta tca gag acg aat aaa aaa gtt ttt ttg gat ttt att   626
Ser Ser Ile Leu Ser Glu Thr Asn Lys Lys Val Phe Leu Asp Phe Ile
            195                 200                 205

tca ttt tgt gaa tca aat aat aaa ttt aca gat ttt ttt aag tta tgg   674
```

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Ser Phe Cys Glu Ser Asn Asn Lys Phe Thr Asp Phe Phe Lys Leu Trp
        210                 215                 220

cga ggt ggg ttt aga tta aat aac agt aga act aaa tta tta tta aaa   722
Arg Gly Gly Phe Arg Leu Asn Asn Ser Arg Thr Lys Leu Leu Leu Lys
    225                 230                 235

ttc tta ata cgg aga aaa ttt agc ga atg att tca ata ctt aca cct   769
Phe Leu Ile Arg Arg Lys Phe Ser    Met Ile Ser Ile Leu Thr Pro
240                 245                 250

act ttt aat cgg caa cat act tta tca agg cta ttc aat tct ctt ata   817
Thr Phe Asn Arg Gln His Thr Leu Ser Arg Leu Phe Asn Ser Leu Ile
255                 260                 265                 270

tta caa act gat aaa gat ttt gag tgg ata ata att gat gat ggt agt   865
Leu Gln Thr Asp Lys Asp Phe Glu Trp Ile Ile Ile Asp Asp Gly Ser
                275                 280                 285

ata gat gca aca gcg gta ctt gta gaa gat ttt aga aaa aaa tgt gat   913
Ile Asp Ala Thr Ala Val Leu Val Glu Asp Phe Arg Lys Lys Cys Asp
            290                 295                 300

ttt gac ttg att tat tgc tat cag gaa aat aat ggt aag ccc atg gct   961
Phe Asp Leu Ile Tyr Cys Tyr Gln Glu Asn Asn Gly Lys Pro Met Ala
        305                 310                 315

tta aac gct ggt gtt aaa gct tgt aga ggc gat tat atc ttt att gtt   1009
Leu Asn Ala Gly Val Lys Ala Cys Arg Gly Asp Tyr Ile Phe Ile Val
    320                 325                 330

gac agt gat gat gca cta act ccc gat gcc ata aaa tta att aaa gaa   1057
Asp Ser Asp Asp Ala Leu Thr Pro Asp Ala Ile Lys Leu Ile Lys Glu
335                 340                 345                 350

tca ata cat gat tgc tta tct gag aag gaa agt ttc agc gga gtc ggt   1105
Ser Ile His Asp Cys Leu Ser Glu Lys Glu Ser Phe Ser Gly Val Gly
                355                 360                 365

ttt aga aaa gca tat ata aaa ggg ggg att att ggt aat gat tta aat   1153
Phe Arg Lys Ala Tyr Ile Lys Gly Gly Ile Ile Gly Asn Asp Leu Asn
            370                 375                 380

aat tct tca gaa cat ata tac tat tta aat gcg act gag att agc aat   1201
Asn Ser Ser Glu His Ile Tyr Tyr Leu Asn Ala Thr Glu Ile Ser Asn
        385                 390                 395

tta ata aat ggt gat gtt gca tat tgt ttt aaa aaa gaa agt ttg gta   1249
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```
Leu Ile Asn Gly Asp Val Ala Tyr Cys Phe Lys Lys Glu Ser Leu Val
    400                 405                 410

aaa aat cca ttc ccc cgt ata gaa gat gaa aaa ttt gtt cca gaa tta   1297
Lys Asn Pro Phe Pro Arg Ile Glu Asp Glu Lys Phe Val Pro Glu Leu
415                 420                 425                 430

tat att tgg aat aaa ata act gac aag gcg aag att cga ttt aac ata   1345
Tyr Ile Trp Asn Lys Ile Thr Asp Lys Ala Lys Ile Arg Phe Asn Ile
                435                 440                 445

agc aaa gtt ata tat ctt tgt gag tat ctt gat gat ggt ctt tct aaa   1393
Ser Lys Val Ile Tyr Leu Cys Glu Tyr Leu Asp Asp Gly Leu Ser Lys
            450                 455                 460

aat ttc cat aac cag ctt aaa aaa tac cca aag ggg ttt aag att tat   1441
Asn Phe His Asn Gln Leu Lys Lys Tyr Pro Lys Gly Phe Lys Ile Tyr
        465                 470                 475

tac aaa gat caa aga aaa cga gag aaa act tat ata aaa aaa aca aag   1489
Tyr Lys Asp Gln Arg Lys Arg Glu Lys Thr Tyr Ile Lys Lys Thr Lys
    480                 485                 490

atg cta att aga tat ttg caa tgt tgt tat tat gag aaa ata aa atg    1536
Met Leu Ile Arg Tyr Leu Gln Cys Cys Tyr Tyr Glu Lys Ile    Met
495                 500                 505

aaa ata cta ttt gtc att aca ggt tta ggc ctt gga ggt gct gag aag   1584
Lys Ile Leu Phe Val Ile Thr Gly Leu Gly Leu Gly Gly Ala Glu Lys
510                 515                 520                 525

cag gtt tgt ctt tta gct gat aaa tta agt tta agc ggg cac cat gta   1632
Gln Val Cys Leu Leu Ala Asp Lys Leu Ser Leu Ser Gly His His Val
                530                 535                 540

aag att att tca ctt gga cat atg tct aat aat aaa gtc ttt cct agc   1680
Lys Ile Ile Ser Leu Gly His Met Ser Asn Asn Lys Val Phe Pro Ser
            545                 550                 555

gaa aat aat gtt aat gtc att aat gta aat atg tca aaa aac att tct   1728
Glu Asn Asn Val Asn Val Ile Asn Val Asn Met Ser Lys Asn Ile Ser
        560                 565                 570

gga gtt ata aaa ggt tgt gtc aga att aga gat gtt ata gct aat ttc   1776
Gly Val Ile Lys Gly Cys Val Arg Ile Arg Asp Val Ile Ala Asn Phe
    575                 580                 585

aaa cca gac att gta cac agt cat atg ttt cat gca aac att atc act   1824
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```
Lys Pro Asp Ile Val His Ser His Met Phe His Ala Asn Ile Ile Thr
590                 595                 600                 605

aga ttg tct gta att gga atc aaa aac aga cct ggt att ata tca act   1872
Arg Leu Ser Val Ile Gly Ile Lys Asn Arg Pro Gly Ile Ile Ser Thr
                610                 615                 620

gca cat aat aaa aat gaa ggt ggg tat ttc aga atg ctc aca tat aga   1920
Ala His Asn Lys Asn Glu Gly Gly Tyr Phe Arg Met Leu Thr Tyr Arg
            625                 630                 635

ata acc gat tgt tta agt gat tgt tgt aca aat gtt agc aaa gaa gca   1968
Ile Thr Asp Cys Leu Ser Asp Cys Cys Thr Asn Val Ser Lys Glu Ala
        640                 645                 650

gtg gat gag ttt tta cgg ata aaa gcc ttt aat ccc gct aaa gca att   2016
Val Asp Glu Phe Leu Arg Ile Lys Ala Phe Asn Pro Ala Lys Ala Ile
    655                 660                 665

act atg tat aat ggg ata gat acc aat aaa ttt aaa ttt gat tta ttg   2064
Thr Met Tyr Asn Gly Ile Asp Thr Asn Lys Phe Lys Phe Asp Leu Leu
670                 675                 680                 685

gca agg agg gaa att cga gac ggt att aat ata aaa aat gat gat ata   2112
Ala Arg Arg Glu Ile Arg Asp Gly Ile Asn Ile Lys Asn Asp Asp Ile
                690                 695                 700

tta tta ctt gct gca ggt cgt tta acg tta gct aaa gat tat cct aat   2160
Leu Leu Leu Ala Ala Gly Arg Leu Thr Leu Ala Lys Asp Tyr Pro Asn
            705                 710                 715

tta ttg aat gca atg act ctg ctt cct gaa cac ttt aaa ctt att att   2208
Leu Leu Asn Ala Met Thr Leu Leu Pro Glu His Phe Lys Leu Ile Ile
        720                 725                 730

att ggt gat ggt gaa ttg cgt gac gaa att aat atg ctt ata aaa aaa   2256
Ile Gly Asp Gly Glu Leu Arg Asp Glu Ile Asn Met Leu Ile Lys Lys
    735                 740                 745

ttg caa tta tct aat agg gtg tcc ttg ttg gga gtt aaa aaa aat att   2304
Leu Gln Leu Ser Asn Arg Val Ser Leu Leu Gly Val Lys Lys Asn Ile
750                 755                 760                 765

gct ccc tat ttt tct gca tgt gat att ttt gtt ctc tct tct cgt tgg   2352
Ala Pro Tyr Phe Ser Ala Cys Asp Ile Phe Val Leu Ser Ser Arg Trp
                770                 775                 780

gaa gga ttt gga tta gtc gtg gca gaa gct atg tca tgt gag cga att   2400
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Glu Gly Phe Gly Leu Val Val Ala Glu Ala Met Ser Cys Glu Arg Ile
            785                 790                 795

gtt gtt ggc acg gat tca ggg gga gta aga gaa gtt att ggt gac gat   2448
Val Val Gly Thr Asp Ser Gly Gly Val Arg Glu Val Ile Gly Asp Asp
        800                 805                 810

gat ttt ctt gta ccc ata tct gat tca aca caa ctt gca agc aaa att   2496
Asp Phe Leu Val Pro Ile Ser Asp Ser Thr Gln Leu Ala Ser Lys Ile
    815                 820                 825

gaa aaa ttg tct ttg agc cag ata cgt gat cac att ggt ttt cgg aat   2544
Glu Lys Leu Ser Leu Ser Gln Ile Arg Asp His Ile Gly Phe Arg Asn
830                 835                 840                 845

cgt gag cgt att tta aaa aat ttc tca ata gat act att att atg cag   2592
Arg Glu Arg Ile Leu Lys Asn Phe Ser Ile Asp Thr Ile Ile Met Gln
                850                 855                 860

tgg caa gaa ctc tat gga act ata att tgc tca aaa cat gaa agg       2637
Trp Gln Glu Leu Tyr Gly Thr Ile Ile Cys Ser Lys His Glu Arg
            865                 870                 875

tagatttata tttggaacgt gtcttttgtt tgaatttaat tcaatctcaa ttgagatttt 2697

tgtatttcaa aaataccatc atagctaacg atgattggta tttattttaa gatgctttct 2757

ataaatatat tgacgttttt aatgcgccga aacgattggg ctgggaacag agaagtaaaa 2817

ctgttttgag aatgaagagt ttttgagatg tttatggata ttaaaaattg atccagtgaa 2877

ttaattattt ataataaatc aagatttaat gttaataaat gataatcttt tctgacactc 2937

atattaatta tgagtggtac gtttggtaaa cggtaaacta ttat atg aca gct aga  2993
                                              Met Thr Ala Arg
                                                          880

aca act aaa gtt ttg cac tta caa tta ctc cca ctc tta agt ggc gtt   3041
Thr Thr Lys Val Leu His Leu Gln Leu Leu Pro Leu Leu Ser Gly Val
                885                 890                 895

caa agg gta aca tta aac gaa att agt gcg tta tat act gat tat gat   3089
Gln Arg Val Thr Leu Asn Glu Ile Ser Ala Leu Tyr Thr Asp Tyr Asp
            900                 905                 910

tat aca cta gtt tgc tca aaa aaa ggt cca cta aca aaa gca ttg ctg   3137
Tyr Thr Leu Val Cys Ser Lys Lys Gly Pro Leu Thr Lys Ala Leu Leu
        915                 920                 925
```

```
gaa tat gat gtc gat tgt cat tgt atc ccc gaa ctt acg aga gaa att   3185
Glu Tyr Asp Val Asp Cys His Cys Ile Pro Glu Leu Thr Arg Glu Ile
    930                 935                 940

acc gta aag aat gat ttt aaa gca ttg ttc aag ctt tat aag ttc ata   3233
Thr Val Lys Asn Asp Phe Lys Ala Leu Phe Lys Leu Tyr Lys Phe Ile
945                 950                 955                 960

aaa aaa gaa aaa ttt gac att gtg cat aca cat tct tca aaa aca ggt   3281
Lys Lys Glu Lys Phe Asp Ile Val His Thr His Ser Ser Lys Thr Gly
                965                 970                 975

att ttg ggg cga gtt gct gcc aaa tta gca cgt gtt gga aag gtg atc   3329
Ile Leu Gly Arg Val Ala Ala Lys Leu Ala Arg Val Gly Lys Val Ile
            980                 985                 990

cac act gta cat ggt ttt tct ttt cca gcc gca tct agt aaa aaa agt   3377
His Thr Val His Gly Phe Ser Phe Pro Ala Ala Ser Ser Lys Lys Ser
        995                1000                1005

tat tac ctt tat ttt ttc atg gaa tgg ata gca aag ttc ttt acg gat   3425
Tyr Tyr Leu Tyr Phe Phe Met Glu Trp Ile Ala Lys Phe Phe Thr Asp
   1010                1015                1020

aag tta atc gtc ttg aat gta gat gat gaa tat ata gca ata aac aaa   3473
Lys Leu Ile Val Leu Asn Val Asp Asp Glu Tyr Ile Ala Ile Asn Lys
1025                1030                1035                1040

tta aaa ttc aag cgg gat aaa gtt ttt tta att cct aat gga gta gac   3521
Leu Lys Phe Lys Arg Asp Lys Val Phe Leu Ile Pro Asn Gly Val Asp
                1045                1050                1055

act gat aag ttt tct cct tta gaa aat aaa att tat agt agc acc ttg   3569
Thr Asp Lys Phe Ser Pro Leu Glu Asn Lys Ile Tyr Ser Ser Thr Leu
            1060                1065                1070

aat cta gta atg gtt ggt aga tta tcc aag caa aaa gat cct gag aca   3617
Asn Leu Val Met Val Gly Arg Leu Ser Lys Gln Lys Asp Pro Glu Thr
        1075                1080                1085

tta ttg ctt gct gtt gaa aaa ctg ctg aat gaa aat gtt aat gtt aag   3665
Leu Leu Leu Ala Val Glu Lys Leu Leu Asn Glu Asn Val Asn Val Lys
   1090                1095                1100

ctg aca ctt gta gga gat ggt gaa cta aaa gaa cag tta gaa agc agg   3713
Leu Thr Leu Val Gly Asp Gly Glu Leu Lys Glu Gln Leu Glu Ser Arg
1105                1110                1115                1120
```

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ttc aaa cgg caa gat gga cgt ata att ttt cat gga tgg tca gat aac   3761
Phe Lys Arg Gln Asp Gly Arg Ile Ile Phe His Gly Trp Ser Asp Asn
                1125                1130                1135

att gtt aat att tta aaa gtt aat gat ctt ttt ata tta cct tct ctt   3809
Ile Val Asn Ile Leu Lys Val Asn Asp Leu Phe Ile Leu Pro Ser Leu
            1140                1145                1150

tgg gag ggt atg cca tta gca att tta gaa gca ttg agc tgt gga ctt   3857
Trp Glu Gly Met Pro Leu Ala Ile Leu Glu Ala Leu Ser Cys Gly Leu
        1155                1160                1165

cca tgt ata gtc act aat att cca ggt aat aat agc tta ata gaa gat   3905
Pro Cys Ile Val Thr Asn Ile Pro Gly Asn Asn Ser Leu Ile Glu Asp
    1170                1175                1180

ggc tat aat ggt tgt ttg ttt gaa att aga gat tgt cag tta tta tct   3953
Gly Tyr Asn Gly Cys Leu Phe Glu Ile Arg Asp Cys Gln Leu Leu Ser
1185                1190                1195                1200

caa aaa atc atg tca tat gtt ggt aag cca gaa ctg att gca cag caa   4001
Gln Lys Ile Met Ser Tyr Val Gly Lys Pro Glu Leu Ile Ala Gln Gln
                1205                1210                1215

tct acc aat gca cga tca ttt att ctg aaa aat tat gga tta gtt aaa   4049
Ser Thr Asn Ala Arg Ser Phe Ile Leu Lys Asn Tyr Gly Leu Val Lys
            1220                1225                1230

aga aat aat aag gtc aga cag cta tat gat aat taaatgaaac cgaaaagtta 4102
Arg Asn Asn Lys Val Arg Gln Leu Tyr Asp Asn
        1235                1240

aaaaagaaca ggtttttcaa agtgaaaata aaattacagt ttttttattg caatgattaa 4162

cgtaacatct gcattacatt caagccgcac aaccccgcgg tgaccacccc tgacaggagt 4222

aaacaatgtc aaagcaacag atcggcgtcg tcggtatggc agtgatggga cgcaacctcg 4282

cgctcaacat cgaaagccgt ggttataccg tctctatttt caaccgttcc cgtgaaaaga 4342

cggaagaagt tattgccgaa aatccaggca agaaactggt tccttactat acggtgaaag 4402

agttcgttga atctcttgaa acgcctcgtc gcatcctgtt aatgggttaa agcaggtgca 4462

ggcacggatg ctgctattga ttccctgaaa ccatatctcg ataaaggcga tatcatcatt 4522

gatgggtggg taataccttc tttcaggaca ccattcgtcg taaccgcgag ctttctgcac 4582
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aaggctttac ttcatcggta cc 4604

<210> 23
<211> 247
<212> PRT
<213> Escherichia coli

<400> 23

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Val Asp Asp Asn Leu Lys Gly Gln Gly Ala Gly Lys Asn Phe Leu Ser
  1               5                  10                  15

Leu Ile Lys Tyr Ser Glu Thr Asp Tyr Thr Ile Tyr Cys Asp Gln Asp
             20                  25                  30

Asp Ile Trp Leu Glu Asn Lys Ile Phe Glu Leu Val Lys Tyr Ala Asn
         35                  40                  45

Glu Ile Lys Leu Asn Val Ser Asp Ala Pro Ser Leu Val Tyr Ala Asp
     50                  55                  60

Gly Tyr Ala Tyr Met Asp Gly Glu Gly Thr Ile Asp Phe Ser Gly Ile
 65                  70                  75                  80

Ser Asn Asn His Ala Asp Gln Leu Lys Asp Phe Leu Phe Phe Asn Gly
                 85                  90                  95

Gly Tyr Gln Gly Cys Ser Ile Met Phe Asn Arg Ala Met Thr Lys Phe
            100                 105                 110

Leu Leu Asn Tyr Arg Gly Phe Val Tyr Leu His Asp Asp Ile Thr Thr
        115                 120                 125

Leu Ala Ala Tyr Ala Leu Gly Lys Val Tyr Phe Leu Pro Lys Tyr Leu
    130                 135                 140

Met Leu Tyr Arg Gln His Thr Asn Ala Val Thr Gly Ile Lys Thr Phe
145                 150                 155                 160

Arg Asn Gly Leu Thr Ser Lys Phe Lys Ser Pro Val Asn Tyr Leu Leu
                165                 170                 175

Ser Arg Lys His Tyr Gln Val Lys Lys Ser Phe Phe Glu Cys Asn Ser
            180                 185                 190

Ser Ile Leu Ser Glu Thr Asn Lys Lys Val Phe Leu Asp Phe Ile Ser
        195                 200                 205
```

```
Phe Cys Glu Ser Asn Asn Lys Phe Thr Asp Phe Phe Lys Leu Trp Arg
    210                 215                 220

Gly Gly Phe Arg Leu Asn Asn Ser Arg Thr Lys Leu Leu Leu Lys Phe
225                 230                 235                 240

Leu Ile Arg Arg Lys Phe Ser
                245
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<210> 24
<211> 261
<212> PRT
<213> Escherichia coli

<400> 24

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Met Ile Ser Ile Leu Thr Pro Thr Phe Asn Arg Gln His Thr Leu Ser
  1               5                  10                  15

Arg Leu Phe Asn Ser Leu Ile Leu Gln Thr Asp Lys Asp Phe Glu Trp
             20                  25                  30

Ile Ile Ile Asp Asp Gly Ser Ile Asp Ala Thr Ala Val Leu Val Glu
         35                  40                  45

Asp Phe Arg Lys Lys Cys Asp Phe Asp Leu Ile Tyr Cys Tyr Gln Glu
     50                  55                  60

Asn Asn Gly Lys Pro Met Ala Leu Asn Ala Gly Val Lys Ala Cys Arg
 65                  70                  75                  80

Gly Asp Tyr Ile Phe Ile Val Asp Ser Asp Asp Ala Leu Thr Pro Asp
                85                  90                  95

Ala Ile Lys Leu Ile Lys Glu Ser Ile His Asp Cys Leu Ser Glu Lys
            100                 105                 110

Glu Ser Phe Ser Gly Val Gly Phe Arg Lys Ala Tyr Ile Lys Gly Gly
        115                 120                 125

Ile Ile Gly Asn Asp Leu Asn Asn Ser Ser Glu His Ile Tyr Tyr Leu
    130                 135                 140

Asn Ala Thr Glu Ile Ser Asn Leu Ile Asn Gly Asp Val Ala Tyr Cys
145                 150                 155                 160

Phe Lys Lys Glu Ser Leu Val Lys Asn Pro Phe Pro Arg Ile Glu Asp
```

165 170 175

Glu Lys Phe Val Pro Glu Leu Tyr Ile Trp Asn Lys Ile Thr Asp Lys
180 185 190

Ala Lys Ile Arg Phe Asn Ile Ser Lys Val Ile Tyr Leu Cys Glu Tyr
195 200 205

Leu Asp Asp Gly Leu Ser Lys Asn Phe His Asn Gln Leu Lys Lys Tyr
210 215 220

Pro Lys Gly Phe Lys Ile Tyr Tyr Lys Asp Gln Arg Lys Arg Glu Lys
225 230 235 240

Thr Tyr Ile Lys Lys Thr Lys Met Leu Ile Arg Tyr Leu Gln Cys Cys
245 250 255

Tyr Tyr Glu Lys Ile
260

<210> 25
<211> 368
<212> PRT
<213> Escherichia coli

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Met Lys Ile Leu Phe Val Ile Thr Gly Leu Gly Leu Gly Gly Ala Glu
1 5 10 15

Lys Gln Val Cys Leu Leu Ala Asp Lys Leu Ser Leu Ser Gly His His
20 25 30

Val Lys Ile Ile Ser Leu Gly His Met Ser Asn Asn Lys Val Phe Pro
35 40 45

Ser Glu Asn Asn Val Asn Val Ile Asn Val Asn Met Ser Lys Asn Ile
50 55 60

Ser Gly Val Ile Lys Gly Cys Val Arg Ile Arg Asp Val Ile Ala Asn
65 70 75 80

Phe Lys Pro Asp Ile Val His Ser His Met Phe His Ala Asn Ile Ile
85 90 95

Thr Arg Leu Ser Val Ile Gly Ile Lys Asn Arg Pro Gly Ile Ile Ser
100 105 110

```
Thr Ala His Asn Lys Asn Glu Gly Gly Tyr Phe Arg Met Leu Thr Tyr
        115                 120                 125

Arg Ile Thr Asp Cys Leu Ser Asp Cys Cys Thr Asn Val Ser Lys Glu
    130                 135                 140

Ala Val Asp Glu Phe Leu Arg Ile Lys Ala Phe Asn Pro Ala Lys Ala
145                 150                 155                 160

Ile Thr Met Tyr Asn Gly Ile Asp Thr Asn Lys Phe Lys Phe Asp Leu
                165                 170                 175

Leu Ala Arg Arg Glu Ile Arg Asp Gly Ile Asn Ile Lys Asn Asp Asp
            180                 185                 190

Ile Leu Leu Leu Ala Ala Gly Arg Leu Thr Leu Ala Lys Asp Tyr Pro
        195                 200                 205

Asn Leu Leu Asn Ala Met Thr Leu Leu Pro Glu His Phe Lys Leu Ile
    210                 215                 220

Ile Ile Gly Asp Gly Glu Leu Arg Asp Glu Ile Asn Met Leu Ile Lys
225                 230                 235                 240

Lys Leu Gln Leu Ser Asn Arg Val Ser Leu Leu Gly Val Lys Lys Asn
                245                 250                 255

Ile Ala Pro Tyr Phe Ser Ala Cys Asp Ile Phe Val Leu Ser Ser Arg
            260                 265                 270

Trp Glu Gly Phe Gly Leu Val Val Ala Glu Ala Met Ser Cys Glu Arg
        275                 280                 285

Ile Val Val Gly Thr Asp Ser Gly Gly Val Arg Glu Val Ile Gly Asp
    290                 295                 300

Asp Asp Phe Leu Val Pro Ile Ser Asp Ser Thr Gln Leu Ala Ser Lys
305                 310                 315                 320

Ile Glu Lys Leu Ser Leu Ser Gln Ile Arg Asp His Ile Gly Phe Arg
                325                 330                 335

Asn Arg Glu Arg Ile Leu Lys Asn Phe Ser Ile Asp Thr Ile Ile Met
            340                 345                 350

Gln Trp Gln Glu Leu Tyr Gly Thr Ile Ile Cys Ser Lys His Glu Arg
        355                 360                 365
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<210> 26
<211> 367
<212> PRT
<213> Escherichia coli

<400> 26

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Met Thr Ala Arg Thr Thr Lys Val Leu His Leu Gln Leu Leu Pro Leu
  1               5                  10                  15

Leu Ser Gly Val Gln Arg Val Thr Leu Asn Glu Ile Ser Ala Leu Tyr
             20                  25                  30

Thr Asp Tyr Asp Tyr Thr Leu Val Cys Ser Lys Lys Gly Pro Leu Thr
         35                  40                  45

Lys Ala Leu Leu Glu Tyr Asp Val Asp Cys His Cys Ile Pro Glu Leu
     50                  55                  60

Thr Arg Glu Ile Thr Val Lys Asn Asp Phe Lys Ala Leu Phe Lys Leu
 65                  70                  75                  80

Tyr Lys Phe Ile Lys Lys Glu Lys Phe Asp Ile Val His Thr His Ser
                 85                  90                  95

Ser Lys Thr Gly Ile Leu Gly Arg Val Ala Ala Lys Leu Ala Arg Val
            100                 105                 110

Gly Lys Val Ile His Thr Val His Gly Phe Ser Phe Pro Ala Ala Ser
        115                 120                 125

Ser Lys Lys Ser Tyr Tyr Leu Tyr Phe Phe Met Glu Trp Ile Ala Lys
    130                 135                 140

Phe Phe Thr Asp Lys Leu Ile Val Leu Asn Val Asp Asp Glu Tyr Ile
145                 150                 155                 160

Ala Ile Asn Lys Leu Lys Phe Lys Arg Asp Lys Val Phe Leu Ile Pro
                165                 170                 175

Asn Gly Val Asp Thr Asp Lys Phe Ser Pro Leu Glu Asn Lys Ile Tyr
            180                 185                 190

Ser Ser Thr Leu Asn Leu Val Met Val Gly Arg Leu Ser Lys Gln Lys
        195                 200                 205

Asp Pro Glu Thr Leu Leu Leu Ala Val Glu Lys Leu Leu Asn Glu Asn
    210                 215                 220
```

```
Val Asn Val Lys Leu Thr Leu Val Gly Asp Gly Glu Leu Lys Glu Gln
225                 230                 235                 240

Leu Glu Ser Arg Phe Lys Arg Gln Asp Gly Arg Ile Ile Phe His Gly
                245                 250                 255

Trp Ser Asp Asn Ile Val Asn Ile Leu Lys Val Asn Asp Leu Phe Ile
            260                 265                 270

Leu Pro Ser Leu Trp Glu Gly Met Pro Leu Ala Ile Leu Glu Ala Leu
        275                 280                 285

Ser Cys Gly Leu Pro Cys Ile Val Thr Asn Ile Pro Gly Asn Asn Ser
    290                 295                 300

Leu Ile Glu Asp Gly Tyr Asn Gly Cys Leu Phe Glu Ile Arg Asp Cys
305                 310                 315                 320

Gln Leu Leu Ser Gln Lys Ile Met Ser Tyr Val Gly Lys Pro Glu Leu
                325                 330                 335

Ile Ala Gln Gln Ser Thr Asn Ala Arg Ser Phe Ile Leu Lys Asn Tyr
            340                 345                 350

Gly Leu Val Lys Arg Asn Asn Lys Val Arg Gln Leu Tyr Asp Asn
        355                 360                 365
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<210> 27
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<212> DNA
<213> Escherichia coli

<220>
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<222> (319)..(1269)

<220>
<221> CDS
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<400> 27

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cc ggg aag cac tcg gcg ctg att gtt gca cat cgt ctg acc acc gcg    47
   Gly Lys His Ser Ala Leu Ile Val Ala His Arg Leu Thr Thr Ala
     1               5                  10                  15
```

```
caa cgc tgc gat ctg att gcc gtt att gat aag ggg tta ctt gcg gaa   95
Gln Arg Cys Asp Leu Ile Ala Val Ile Asp Lys Gly Leu Leu Ala Glu
                 20                  25                  30

tac gga acc cac gaa cag ctg tta tct gcg ggc ggc ctc tat acc cgc  143
Tyr Gly Thr His Glu Gln Leu Leu Ser Ala Gly Gly Leu Tyr Thr Arg
             35                  40                  45

tta tgg cat gac agc gtc agc agt act gct ctc cat cgc cag cac aac  191
Leu Trp His Asp Ser Val Ser Ser Thr Ala Leu His Arg Gln His Asn
         50                  55                  60

atg aag gag gaa acc ccg gga tag ttactggaca cgtaatgtat taaaaacaca  245
Met Lys Glu Glu Thr Pro Gly
     65                  70

gtcagaagcg gcggtaccgt gaatagccgc tttaattatt tatactgaca tccttaattt 305

ttaaagagta tga atg ctg aac atg caa caa cat ctc tct gct atc gcc    354
               Met Leu Asn Met Gln Gln His Leu Ser Ala Ile Ala
                           75                  80

agc ctg cgc aac caa ctg gca gcg ggc cac att gct aac ctt act gac   402
Ser Leu Arg Asn Gln Leu Ala Ala Gly His Ile Ala Asn Leu Thr Asp
     85                  90                  95

ttc tgg cgc gaa gct gag tcg ctg aat gtt cct ctt gtg acg cca gtc   450
Phe Trp Arg Glu Ala Glu Ser Leu Asn Val Pro Leu Val Thr Pro Val
100                 105                 110                 115

gaa gga gcg gaa gat gag cga gaa gtg acc ttt ctg tgg cgc gcc cga   498
Glu Gly Ala Glu Asp Glu Arg Glu Val Thr Phe Leu Trp Arg Ala Arg
                120                 125                 130

cat cct ctg cag ggc gtt tat ctg cgt ctg aac cgg gtg acg gat aaa   546
His Pro Leu Gln Gly Val Tyr Leu Arg Leu Asn Arg Val Thr Asp Lys
            135                 140                 145

gag cac gta gaa aaa gga atg atg agc gcc ctt ccc gaa acg gat atc   594
Glu His Val Glu Lys Gly Met Met Ser Ala Leu Pro Glu Thr Asp Ile
        150                 155                 160

tgg aca ctg aca ctg cgt tta ccc gca agt tac tgc ggc tcc tat tcg   642
Trp Thr Leu Thr Leu Arg Leu Pro Ala Ser Tyr Cys Gly Ser Tyr Ser
    165                 170                 175

ctg ctg gaa atc ccc ccc ggc act acg gct gag acg att gca ctg tcc   690
Leu Leu Glu Ile Pro Pro Gly Thr Thr Ala Glu Thr Ile Ala Leu Ser
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180                 185                 190                 195

gga ggc cgt ttt gcc acc ctt gcc gga aag gcc gat ccg cta aac aaa   738
Gly Gly Arg Phe Ala Thr Leu Ala Gly Lys Ala Asp Pro Leu Asn Lys
                200                 205                 210

atg ccg gag atc aac gtt cgg gga aac gca aag gaa tca gtg ctg aca   786
Met Pro Glu Ile Asn Val Arg Gly Asn Ala Lys Glu Ser Val Leu Thr
            215                 220                 225

ctt gat aaa gct ccc gcc ctg tcg gaa tgg aac ggc ggc ttc cac acc   834
Leu Asp Lys Ala Pro Ala Leu Ser Glu Trp Asn Gly Gly Phe His Thr
        230                 235                 240

gga caa ctg ctt acc tcc atg cgc att atc gcc ggg aaa tct cgc cag   882
Gly Gln Leu Leu Thr Ser Met Arg Ile Ile Ala Gly Lys Ser Arg Gln
    245                 250                 255

gtt cgg ctc tat att ccg gat gtt gat att tct cag ccc ctc ggg ctg   930
Val Arg Leu Tyr Ile Pro Asp Val Asp Ile Ser Gln Pro Leu Gly Leu
260                 265                 270                 275

gtc gtg ctg ccc gat ggt gaa acc tgg ttt gat cac ctt ggc gta tgc   978
Val Val Leu Pro Asp Gly Glu Thr Trp Phe Asp His Leu Gly Val Cys
                280                 285                 290

gcg gca att gac gcc gcc ata aat aat ggg cgc atc gtg ccc gtg gct   1026
Ala Ala Ile Asp Ala Ala Ile Asn Asn Gly Arg Ile Val Pro Val Ala
            295                 300                 305

gta ctg ggc att gac aac att aat gaa cat gaa cgc act gag ata ctc   1074
Val Leu Gly Ile Asp Asn Ile Asn Glu His Glu Arg Thr Glu Ile Leu
        310                 315                 320

ggc ggg cgc agc aaa ctg ata aag gat atc gcc gga cat ctg ctg ccg   1122
Gly Gly Arg Ser Lys Leu Ile Lys Asp Ile Ala Gly His Leu Leu Pro
    325                 330                 335

atg att cgc gct gaa caa ccg cag cgt cag tgg gca gac cgt tcg cgc   1170
Met Ile Arg Ala Glu Gln Pro Gln Arg Gln Trp Ala Asp Arg Ser Arg
340                 345                 350                 355

aca gtg ctg gcc ggg cag agc ctc ggc ggg atc agt gcg cta atg ggg   1218
Thr Val Leu Ala Gly Gln Ser Leu Gly Gly Ile Ser Ala Leu Met Gly
                360                 365                 370

gct cgt tac gca ccg gaa acg ttc ggt ctg gtg ctc agc cac tct cct   1266
Ala Arg Tyr Ala Pro Glu Thr Phe Gly Leu Val Leu Ser His Ser Pro
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Gln

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<213> Escherichia coli

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Arg Cys Asp Leu Ile Ala Val Ile Asp Lys Gly Leu Leu Ala Glu Tyr
20 25 30

Gly Thr His Glu Gln Leu Leu Ser Ala Gly Gly Leu Tyr Thr Arg Leu
35 40 45

Trp His Asp Ser Val Ser Ser Thr Ala Leu His Arg Gln His Asn Met
50 55 60

Lys Glu Glu Thr Pro Gly
65 70

<210> 29
<211> 317
<212> PRT
<213> Escherichia coli

<400> 29
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Gln Leu Ala Ala Gly His Ile Ala Asn Leu Thr Asp Phe Trp Arg Glu
20 25 30

Ala Glu Ser Leu Asn Val Pro Leu Val Thr Pro Val Glu Gly Ala Glu
35 40 45

Asp Glu Arg Glu Val Thr Phe Leu Trp Arg Ala Arg His Pro Leu Gln
50 55 60

Gly Val Tyr Leu Arg Leu Asn Arg Val Thr Asp Lys Glu His Val Glu
65 70 75 80

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Lys Gly Met Met Ser Ala Leu Pro Glu Thr Asp Ile Trp Thr Leu Thr
                85                  90                  95

Leu Arg Leu Pro Ala Ser Tyr Cys Gly Ser Tyr Ser Leu Leu Glu Ile
            100                 105                 110

Pro Pro Gly Thr Thr Ala Glu Thr Ile Ala Leu Ser Gly Gly Arg Phe
        115                 120                 125

Ala Thr Leu Ala Gly Lys Ala Asp Pro Leu Asn Lys Met Pro Glu Ile
    130                 135                 140

Asn Val Arg Gly Asn Ala Lys Glu Ser Val Leu Thr Leu Asp Lys Ala
145                 150                 155                 160

Pro Ala Leu Ser Glu Trp Asn Gly Gly Phe His Thr Gly Gln Leu Leu
                165                 170                 175

Thr Ser Met Arg Ile Ile Ala Gly Lys Ser Arg Gln Val Arg Leu Tyr
            180                 185                 190

Ile Pro Asp Val Asp Ile Ser Gln Pro Leu Gly Leu Val Val Leu Pro
        195                 200                 205

Asp Gly Glu Thr Trp Phe Asp His Leu Gly Val Cys Ala Ala Ile Asp
    210                 215                 220

Ala Ala Ile Asn Asn Gly Arg Ile Val Pro Val Ala Val Leu Gly Ile
225                 230                 235                 240

Asp Asn Ile Asn Glu His Glu Arg Thr Glu Ile Leu Gly Gly Arg Ser
                245                 250                 255

Lys Leu Ile Lys Asp Ile Ala Gly His Leu Leu Pro Met Ile Arg Ala
            260                 265                 270

Glu Gln Pro Gln Arg Gln Trp Ala Asp Arg Ser Arg Thr Val Leu Ala
        275                 280                 285

Gly Gln Ser Leu Gly Gly Ile Ser Ala Leu Met Gly Ala Arg Tyr Ala
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agc gaa acc gat acc tca tgg gtg agt gag cat ctg ctt tct gcc cca   96
Ser Glu Thr Asp Thr Ser Trp Val Ser Glu His Leu Leu Ser Ala Pro
             20                  25                  30

ccg cag ggc gta cgt atc agc ctg tgc gtg gga tcg ctg gaa ggt tcg   144
Pro Gln Gly Val Arg Ile Ser Leu Cys Val Gly Ser Leu Glu Gly Ser
         35                  40                  45

aca gtg cct cac gtt cag cag ctt cac cag cgg ctg att acc gct ggc   192
Thr Val Pro His Val Gln Gln Leu His Gln Arg Leu Ile Thr Ala Gly
     50                  55                  60

gtc gaa agc cat tgc gca atc tac acc ggt ggt cac gat tac gca tgg   240
Val Glu Ser His Cys Ala Ile Tyr Thr Gly Gly His Asp Tyr Ala Trp
 65                  70                  75                  80

tgg cgc ggt gca ctg att gac ggg att ggt tta cta cag ggt tga       285
Trp Arg Gly Ala Leu Ile Asp Gly Ile Gly Leu Leu Gln Gly
                 85                  90                  95

gttgacccac aaacactttc aggaaacggt acagacttcc tgaataaatc aaatagtcac 345

ctgcggaaaa ggaataatca tcag atg tat gcc cgc gag tat cgc tca aca    396
                          Met Tyr Ala Arg Glu Tyr Arg Ser Thr
                                      100

cgc ccg cat aaa gcg att ttc ttt cat ctt tct tgc ctc acc ctt atc   444
Arg Pro His Lys Ala Ile Phe Phe His Leu Ser Cys Leu Thr Leu Ile
105                 110                 115                 120
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tgt agt gcg caa gtt tat gcg aag ccg gat atg cgg cca ctg ggg ccg   492
Cys Ser Ala Gln Val Tyr Ala Lys Pro Asp Met Arg Pro Leu Gly Pro
                125                 130                 135

aat ata gcc gat aaa ggc tcc gtg ttt tac cat ttc agc gtc acc tct   540
Asn Ile Ala Asp Lys Gly Ser Val Phe Tyr His Phe Ser Val Thr Ser
            140                 145                 150

ttc gac tct gtc gat ggc aca cgc cat tat cgg gta tgg acg gcc gtg   588
Phe Asp Ser Val Asp Gly Thr Arg His Tyr Arg Val Trp Thr Ala Val
        155                 160                 165

ccg aat aca acc gca ccg gca tcg ggt tac ccg att tta tat atg ctt   636
Pro Asn Thr Thr Ala Pro Ala Ser Gly Tyr Pro Ile Leu Tyr Met Leu
    170                 175                 180

gac ggt aac gca gtt atg gat cgc ctg gat gac gaa ctg ctc aaa caa   684
Asp Gly Asn Ala Val Met Asp Arg Leu Asp Asp Glu Leu Leu Lys Gln
185                 190                 195                 200

ttg tca gaa aaa aca ccg cca gtg atc gtg gct gtc ggg tat cag acc   732
Leu Ser Glu Lys Thr Pro Pro Val Ile Val Ala Val Gly Tyr Gln Thr
                205                 210                 215

aac ctc cct ttc gat ctc aac agc agg gct tac gac tat acg cca gca   780
Asn Leu Pro Phe Asp Leu Asn Ser Arg Ala Tyr Asp Tyr Thr Pro Ala
            220                 225                 230

gca gaa agc aga aaa aca gat ctc cac tca ggg cgt ttt agc cgt aag   828
Ala Glu Ser Arg Lys Thr Asp Leu His Ser Gly Arg Phe Ser Arg Lys
        235                 240                 245

agt ggt ggc agc aac aac ttc cgc cag tta ctg gaa acg cgt att gcc   876
Ser Gly Gly Ser Asn Asn Phe Arg Gln Leu Leu Glu Thr Arg Ile Ala
    250                 255                 260

cca aaa gtg gaa cag gga ctg aat atc gat cgg caa cgc cgc ggc tta   924
Pro Lys Val Glu Gln Gly Leu Asn Ile Asp Arg Gln Arg Arg Gly Leu
265                 270                 275                 280

tgg ggg cac tcc tac ggc ggc ctc ttc gtg ctg gat tcc tgg ctg tcc   972
Trp Gly His Ser Tyr Gly Gly Leu Phe Val Leu Asp Ser Trp Leu Ser
                285                 290                 295

tcc tct tac ttc cgg tcg tac tac agc gcc agc ccg tcg ttg ggc aga  1020
Ser Ser Tyr Phe Arg Ser Tyr Tyr Ser Ala Ser Pro Ser Leu Gly Arg
            300                 305                 310
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ggt tat gat gct ttg cta agc cgc gtt acg gcg gtt gag cct ctg caa   1068
Gly Tyr Asp Ala Leu Leu Ser Arg Val Thr Ala Val Glu Pro Leu Gln
        315                 320                 325

ttc tgc gcc aaa cac ctg gcg ata atg gaa ggc tcg gcg aca cag ggt   1116
Phe Cys Ala Lys His Leu Ala Ile Met Glu Gly Ser Ala Thr Gln Gly
    330                 335                 340

gat aac cgg gaa acg cat gct gtc ggg gtg ctg tcg aaa att cat acc   1164
Asp Asn Arg Glu Thr His Ala Val Gly Val Leu Ser Lys Ile His Thr
345                 350                 355                 360

acc ctc act ata ctg aaa gat aaa ggc gtc aat gcc gta ttt tgg gat   1212
Thr Leu Thr Ile Leu Lys Asp Lys Gly Val Asn Ala Val Phe Trp Asp
                365                 370                 375

ttc ccc aac ctg gga cac ggg ccg atg ttc aat gcc tcc ttt cgc cag   1260
Phe Pro Asn Leu Gly His Gly Pro Met Phe Asn Ala Ser Phe Arg Gln
            380                 385                 390

gca ctg tta gat atc agt ggt gaa aac gca aat tac aca gca ggt tgt   1308
Ala Leu Leu Asp Ile Ser Gly Glu Asn Ala Asn Tyr Thr Ala Gly Cys
        395                 400                 405

cat gag tta agc cac taa acactgcccg cttttacgcg ggcagtacgc          1356
His Glu Leu Ser His
    410

ctgaaacact acgatcagaa tgatgcggta actccggcat agtaagcccg gcctggctcg 1416

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<400> 31

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Ser Glu Thr Asp Thr Ser Trp Val Ser Glu His Leu Leu Ser Ala Pro
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Pro Gln Gly Val Arg Ile Ser Leu Cys Val Gly Ser Leu Glu Gly Ser
35 40 45

Thr Val Pro His Val Gln Gln Leu His Gln Arg Leu Ile Thr Ala Gly
50 55 60

Val Glu Ser His Cys Ala Ile Tyr Thr Gly Gly His Asp Tyr Ala Trp
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Trp Arg Gly Ala Leu Ile Asp Gly Ile Gly Leu Leu Gln Gly
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<210> 32
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<212> PRT
<213> Escherichia coli

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Phe His Leu Ser Cys Leu Thr Leu Ile Cys Ser Ala Gln Val Tyr Ala
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Lys Pro Asp Met Arg Pro Leu Gly Pro Asn Ile Ala Asp Lys Gly Ser
         35                  40                  45

Val Phe Tyr His Phe Ser Val Thr Ser Phe Asp Ser Val Asp Gly Thr
     50                  55                  60

Arg His Tyr Arg Val Trp Thr Ala Val Pro Asn Thr Thr Ala Pro Ala
 65                  70                  75                  80

Ser Gly Tyr Pro Ile Leu Tyr Met Leu Asp Gly Asn Ala Val Met Asp
                 85                  90                  95

Arg Leu Asp Asp Glu Leu Leu Lys Gln Leu Ser Glu Lys Thr Pro Pro
            100                 105                 110

Val Ile Val Ala Val Gly Tyr Gln Thr Asn Leu Pro Phe Asp Leu Asn
        115                 120                 125

Ser Arg Ala Tyr Asp Tyr Thr Pro Ala Ala Glu Ser Arg Lys Thr Asp
    130                 135                 140

Leu His Ser Gly Arg Phe Ser Arg Lys Ser Gly Gly Ser Asn Asn Phe
145                 150                 155                 160

Arg Gln Leu Leu Glu Thr Arg Ile Ala Pro Lys Val Glu Gln Gly Leu
                165                 170                 175

Asn Ile Asp Arg Gln Arg Arg Gly Leu Trp Gly His Ser Tyr Gly Gly
            180                 185                 190

Leu Phe Val Leu Asp Ser Trp Leu Ser Ser Ser Tyr Phe Arg Ser Tyr
        195                 200                 205

Tyr Ser Ala Ser Pro Ser Leu Gly Arg Gly Tyr Asp Ala Leu Leu Ser
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Arg Val Thr Ala Val Glu Pro Leu Gln Phe Cys Ala Lys His Leu Ala
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Ile Met Glu Gly Ser Ala Thr Gln Gly Asp Asn Arg Glu Thr His Ala
245 250 255

Val Gly Val Leu Ser Lys Ile His Thr Thr Leu Thr Ile Leu Lys Asp
260 265 270

Lys Gly Val Asn Ala Val Phe Trp Asp Phe Pro Asn Leu Gly His Gly
275 280 285

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Glu Asn Ala Asn Tyr Thr Ala Gly Cys His Glu Leu Ser His
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    1               5                  10                  15

ctg gtg ggc ggc aat atg gca ggc gcg ctg gca ggt gct tca gcg ccg   97
Leu Val Gly Gly Asn Met Ala Gly Ala Leu Ala Gly Ala Ser Ala Pro
             20                  25                  30

gag ctg gcg aac atc atc ggt cat cac gcg ggt att gat gac aat aca   145
Glu Leu Ala Asn Ile Ile Gly His His Ala Gly Ile Asp Asp Asn Thr
         35                  40                  45

gcg gca aaa gcc att gcc cat gcc att ctc ggt ggt gtg aca gca gcc   193
Ala Ala Lys Ala Ile Ala His Ala Ile Leu Gly Gly Val Thr Ala Ala
     50                  55                  60

ctt cag ggc aac agt gcg gca gca ggc gca att ggt gcg ggt act ggt   241
Leu Gln Gly Asn Ser Ala Ala Ala Gly Ala Ile Gly Ala Gly Thr Gly
 65                  70                  75                  80

gaa gtg atc gcg tca gcc att gcg aaa agc ctc tac ccg ggc gta gat   289
Glu Val Ile Ala Ser Ala Ile Ala Lys Ser Leu Tyr Pro Gly Val Asp
                 85                  90                  95

ccg tcg aaa ctg aca gaa gat cag aag caa act gta agc acg ctg gca   337
Pro Ser Lys Leu Thr Glu Asp Gln Lys Gln Thr Val Ser Thr Leu Ala
            100                 105                 110

acg ctg tca gcg ggt atg gcc ggc ggc att gcc agt ggc gat gtg gct   385
Thr Leu Ser Ala Gly Met Ala Gly Gly Ile Ala Ser Gly Asp Val Ala
        115                 120                 125

ggc gcg gct gct gga gct ggt gcc ggg aag aac gtt gtt gag aat aat   433
Gly Ala Ala Ala Gly Ala Gly Ala Gly Lys Asn Val Val Glu Asn Asn
    130                 135                 140

gcg ctg agt ctg gtt gcc aga ggc tgt gcg gtc gca gca cct tgc agg   481
Ala Leu Ser Leu Val Ala Arg Gly Cys Ala Val Ala Ala Pro Cys Arg
145                 150                 155                 160

act aaa gtt gca gag cag ttg cta gaa atc ggg gcg aaa gcg ggc atg   529
Thr Lys Val Ala Glu Gln Leu Leu Glu Ile Gly Ala Lys Ala Gly Met
                165                 170                 175

gcc ggg ctt gcc ggg gcg gca gtc aag gat atg gcc gac agg atg acc   577
Ala Gly Leu Ala Gly Ala Ala Val Lys Asp Met Ala Asp Arg Met Thr
            180                 185                 190
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tcc gat gaa ctg gag cat ctg att acc ctg caa atg atg ggt aat gat   625
Ser Asp Glu Leu Glu His Leu Ile Thr Leu Gln Met Met Gly Asn Asp
        195                 200                 205

gag atc act act aag tat ctc agt tcg ttg cat gat aag tac ggt tcc   673
Glu Ile Thr Thr Lys Tyr Leu Ser Ser Leu His Asp Lys Tyr Gly Ser
    210                 215                 220

ggg gct gcc tcg aat ccg aat atc ggt aaa gat ctg acc gat gcg gaa   721
Gly Ala Ala Ser Asn Pro Asn Ile Gly Lys Asp Leu Thr Asp Ala Glu
225                 230                 235                 240

aaa gta gaa ctg ggc ggt tcc ggc tca gga acc ggt aca cca cca cca   769
Lys Val Glu Leu Gly Gly Ser Gly Ser Gly Thr Gly Thr Pro Pro Pro
                245                 250                 255

tcg gaa aat gat cct aag cag caa aat gaa aaa act gta gat aag ctt   817
Ser Glu Asn Asp Pro Lys Gln Gln Asn Glu Lys Thr Val Asp Lys Leu
            260                 265                 270

aat cag aag caa gaa agt gcg att aag aag atc gat aac act ata aaa   865
Asn Gln Lys Gln Glu Ser Ala Ile Lys Lys Ile Asp Asn Thr Ile Lys
        275                 280                 285

aat gct ctg aaa gat cat gat att att gga act ctc aag gat atg gat   913
Asn Ala Leu Lys Asp His Asp Ile Ile Gly Thr Leu Lys Asp Met Asp
    290                 295                 300

ggt aag cca gtt cct aaa gag aat gga gga tat tgg gat cat atg cag   961
Gly Lys Pro Val Pro Lys Glu Asn Gly Gly Tyr Trp Asp His Met Gln
305                 310                 315                 320

gaa atg caa aat acg ctc aga gga tta aga aat cat gcg gat acg ttg   1009
Glu Met Gln Asn Thr Leu Arg Gly Leu Arg Asn His Ala Asp Thr Leu
                325                 330                 335

aaa aac gtc aac aat cct gaa gct cag gct gcg tat ggc aga gca aca   1057
Lys Asn Val Asn Asn Pro Glu Ala Gln Ala Ala Tyr Gly Arg Ala Thr
            340                 345                 350

gat gct att aat aaa ata gaa tca gcc ttg aaa gga tat gga at atg    1104
Asp Ala Ile Asn Lys Ile Glu Ser Ala Leu Lys Gly Tyr Gly    Met
        355                 360                 365

att acc tta cgt aaa ttg att gga aac atc aat atg aca aaa gag cct   1152
Ile Thr Leu Arg Lys Leu Ile Gly Asn Ile Asn Met Thr Lys Glu Pro
        370                 375                 380
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gag caa caa tca ccg ctt gaa ctc tgg ttc gaa cgt atc ata gat gtg   1200
Glu Gln Gln Ser Pro Leu Glu Leu Trp Phe Glu Arg Ile Ile Asp Val
    385                 390                 395

cct ctt gaa aag tta aca gtg gaa gat ctt tgc cgc gct atc cga caa   1248
Pro Leu Glu Lys Leu Thr Val Glu Asp Leu Cys Arg Ala Ile Arg Gln
400                 405                 410                 415

aat tta tgt att gat cag ttg atg cca aga gtg ttg gaa gtt cta act   1296
Asn Leu Cys Ile Asp Gln Leu Met Pro Arg Val Leu Glu Val Leu Thr
                420                 425                 430

aaa gag ccg tta gcg ggt gaa tat tac gat ggt gaa cta att gca gct   1344
Lys Glu Pro Leu Ala Gly Glu Tyr Tyr Asp Gly Glu Leu Ile Ala Ala
            435                 440                 445

tta tca acg ata aaa gga gaa gat cta aaa gat cag aaa agt acc ttt   1392
Leu Ser Thr Ile Lys Gly Glu Asp Leu Lys Asp Gln Lys Ser Thr Phe
        450                 455                 460

acc caa ata agg caa ctt ata aac cag cta gaa ccg tca gat att aac   1440
Thr Gln Ile Arg Gln Leu Ile Asn Gln Leu Glu Pro Ser Asp Ile Asn
    465                 470                 475

gat gat tta aga aaa gat ata tta aaa atc aat cag ata att gta       1485
Asp Asp Leu Arg Lys Asp Ile Leu Lys Ile Asn Gln Ile Ile Val
480                 485                 490

taactaatcc cggccactga gccgagatct tctttgtgtg ccgggcatgt tcagcagctt 1545

gggggtgaaa gtcccctgtc cagcctg atg gtg gcg aag gcg ttc gcg tac gca 1599
                              Met Val Ala Lys Ala Phe Ala Tyr Ala
                              495                 500

ctt aac cag tgg ccg gca ctg acg tac tat gcg aac gat ggc tgg gtg   1647
Leu Asn Gln Trp Pro Ala Leu Thr Tyr Tyr Ala Asn Asp Gly Trp Val
    505                 510                 515

gaa atc gac aac aac atc gct gaa aat gcc ctg cgg gcg gtc agt ctg   1695
Glu Ile Asp Asn Asn Ile Ala Glu Asn Ala Leu Arg Ala Val Ser Leu
520                 525                 530                 535

ggt cgt aaa aac ttc ctg ttc ttc ggc tct gac cat ggt ggt gag cgg   1743
Gly Arg Lys Asn Phe Leu Phe Phe Gly Ser Asp His Gly Gly Glu Arg
                540                 545                 550

gga gcg cta ctg tac agc ctg atc ggg acg tgc aaa ctg aat gac gtg   1791
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Gly Ala Leu Leu Tyr Ser Leu Ile Gly Thr Cys Lys Leu Asn Asp Val
            555                 560                 565

gat cca gaa agc tac ctt cgc cat gtg ctt gcc gtc ata gca gac tgg   1839
Asp Pro Glu Ser Tyr Leu Arg His Val Leu Ala Val Ile Ala Asp Trp
        570                 575                 580

ccg gtc aac cgg gtc agc gaa ctg ctt ccg tgg cgc ata gca ctg cca   1887
Pro Val Asn Arg Val Ser Glu Leu Leu Pro Trp Arg Ile Ala Leu Pro
    585                 590                 595

gct gaa taacacatcc ccgtcaatac ggccctcgct gtacgcttac agaaa atg ctg 1944
Ala Glu                                                 Met Leu
600

atg tct gta cag aaa gaa aag aac gtc gca gag agt gtg gta tct gaa   1992
Met Ser Val Gln Lys Glu Lys Asn Val Ala Glu Ser Val Val Ser Glu
    605                 610                 615

acg cat acc ggc gac agc gta tat gct tcc ctg ttt gaa aaa att aac   2040
Thr His Thr Gly Asp Ser Val Tyr Ala Ser Leu Phe Glu Lys Ile Asn
620                 625                 630                 635

ctg aat ccg gta tct gcc ctg agt gca ctg gat aac cct ttc cgg tca   2088
Leu Asn Pro Val Ser Ala Leu Ser Ala Leu Asp Asn Pro Phe Arg Ser
                640                 645                 650

gca gat aac gcg act ggc aga att acc tcc agc ata caa cct gcg gtg   2136
Ala Asp Asn Ala Thr Gly Arg Ile Thr Ser Ser Ile Gln Pro Ala Val
            655                 660                 665

cag tgc gca gct gct gca gca act gag ggt tct tgt ccc cgg caa tcc   2184
Gln Cys Ala Ala Ala Ala Ala Thr Glu Gly Ser Cys Pro Arg Gln Ser
        670                 675                 680

ccg tgt tca gga a atg gtg gat aac tgg cag aag agt gta agg agt cgt 2233
Pro Cys Ser Gly   Met Val Asp Asn Trp Gln Lys Ser Val Arg Ser Arg
    685                 690                 695

gcg ctc ccg gaa gag gcg atg acg ggc tgg aac gaa ggc atg atc cgc   2281
Ala Leu Pro Glu Glu Ala Met Thr Gly Trp Asn Glu Gly Met Ile Arg
700                 705                 710                 715

tta cag cag ttg gct gag cgc ctg aac cgt cag gat gaa cag cgg gga   2329
Leu Gln Gln Leu Ala Glu Arg Leu Asn Arg Gln Asp Glu Gln Arg Gly
                720                 725                 730

aaa tac atg acg gtc agt gaa ctg aaa acg gag gtg ttt ggc atc atg   2377
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Lys Tyr Met Thr Val Ser Glu Leu Lys Thr Glu Val Phe Gly Ile Met
            735                 740                 745

cag gct ttt aac cgg cat atc ccg gcg gaa gag cag tta cgt cgc tac   2425
Gln Ala Phe Asn Arg His Ile Pro Ala Glu Glu Gln Leu Arg Arg Tyr
        750                 755                 760

ggt gaa gtc cgt aac cag aat ggc agt gaa cag cag caa aaa cag gct   2473
Gly Glu Val Arg Asn Gln Asn Gly Ser Glu Gln Gln Gln Lys Gln Ala
    765                 770                 775

gaa atg gcg cta aat cag tta att aac cgt tat cag atg ata cgt gca   2521
Glu Met Ala Leu Asn Gln Leu Ile Asn Arg Tyr Gln Met Ile Arg Ala
780                 785                 790                 795

ggc aaa caa tagtggtagc cataatgcag gagcaaagcc tgaatcagga          2570
Gly Lys Gln

agagttattc tgactgagtt tggttttctg gcgattcttg tg atg gtg gga tgt    2624
                                              Met Val Gly Cys
                                                  800

gct tgg tta gct gaa cag gcc ttt tcc gac cat gcg ctt tca cca cac   2672
Ala Trp Leu Ala Glu Gln Ala Phe Ser Asp His Ala Leu Ser Pro His
        805                 810                 815

agt gct tgg ccg tac agt gca tcg cgc gat gcc ggg ctg gcc gat acg   2720
Ser Ala Trp Pro Tyr Ser Ala Ser Arg Asp Ala Gly Leu Ala Asp Thr
    820                 825                 830

ggc gcg ggc ggc tat ccc act tgt aaa cag cgg tgg gcc gac gac acc   2768
Gly Ala Gly Gly Tyr Pro Thr Cys Lys Gln Arg Trp Ala Asp Asp Thr
835                 840                 845                 850

gtt ggg ctg aaa gcc cgt cta ctg caa ctt cct gcc cta gat atc tgg   2816
Val Gly Leu Lys Ala Arg Leu Leu Gln Leu Pro Ala Leu Asp Ile Trp
                855                 860                 865

acg gcg ttt aaa aaa atc gac cag tcg cag gta gtg tat gaa gag gcc   2864
Thr Ala Phe Lys Lys Ile Asp Gln Ser Gln Val Val Tyr Glu Glu Ala
            870                 875                 880

gtg ctg cgc tcg cgg gtc agt gaa cga aat atg cag gta tcg cag aat   2912
Val Leu Arg Ser Arg Val Ser Glu Arg Asn Met Gln Val Ser Gln Asn
        885                 890                 895

ggg cgc gtt tat cca agc tat ggc ggt aac gtt gat ggc acc gtc gcc   2960
Gly Arg Val Tyr Pro Ser Tyr Gly Gly Asn Val Asp Gly Thr Val Ala
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    900                 905                 910

aat gcc gcc acc cgg ttg gca tcc ggc gct aga aat atc ctc ggc agc   3008
Asn Ala Ala Thr Arg Leu Ala Ser Gly Ala Arg Asn Ile Leu Gly Ser
915                 920                 925                 930

ata gcg gca tgt acg gca ttc gac agc gtg cgt taggcactac cg atg gta 3059
Ile Ala Ala Cys Thr Ala Phe Asp Ser Val Arg               Met Val
                935                 940

cag gcg cag ctg caa ata gcg ctg gtg atc tgt att ccg ctg ata acg   3107
Gln Ala Gln Leu Gln Ile Ala Leu Val Ile Cys Ile Pro Leu Ile Thr
    945                 950                 955

ctc tgt tcg gcg tgg gat gtg aaa gta gtg atg acg ctg acg ttt gtg   3155
Leu Cys Ser Ala Trp Asp Val Lys Val Val Met Thr Leu Thr Phe Val
960                 965                 970                 975

cag ttt gca cta ttt ttc ctc acc ttt tgg tgg gaa ctg gca cgg tgg   3203
Gln Phe Ala Leu Phe Phe Leu Thr Phe Trp Trp Glu Leu Ala Arg Trp
                980                 985                 990

ctt gat agc tgg ctg ctg gat gtg ctc tac aac agc gat acc cac agt   3251
Leu Asp Ser Trp Leu Leu Asp Val Leu Tyr Asn Ser Asp Thr His Ser
            995                1000                1005

agc tgg aat tta gcc ggg atc cag aat acg cag gat gac gtg att atc   3299
Ser Trp Asn Leu Ala Gly Ile Gln Asn Thr Gln Asp Asp Val Ile Ile
       1010                1015                1020

aat ctg gtg atg agg ttg atg ttt ctg gtg ttg ccg aca ttc tgg ctg   3347
Asn Leu Val Met Arg Leu Met Phe Leu Val Leu Pro Thr Phe Trp Leu
   1025                1030                1035

ggg gcg atg acg tgg gct gga gtg agg gtt ggc gtg gcg ctg aat gga   3395
Gly Ala Met Thr Trp Ala Gly Val Arg Val Gly Val Ala Leu Asn Gly
1040                1045                1050                1055

gcg ctg gcg gga tgattgggag gtgattcgcc aatctcactt tcctatacac       3447
Ala Leu Ala Gly

atataaaatg ta atg aaa tat ctc ttt ttt gag aat ata cat tct ata ttt 3498
             Met Lys Tyr Leu Phe Phe Glu Asn Ile His Ser Ile Phe
            1060                1065                1070

tta aca ttc agt ctc ttc cga aca tct gtg tcg cct gat ttc cca atg   3546
Leu Thr Phe Ser Leu Phe Arg Thr Ser Val Ser Pro Asp Phe Pro Met
       1075                1080                1085
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att ttt gca ttg ccc tca atc att tta ggt caa ttt acg acc aac caa   3594
Ile Phe Ala Leu Pro Ser Ile Ile Leu Gly Gln Phe Thr Thr Asn Gln
   1090                1095                1100

tta act aac ttt gtg ata tgt atg ggt aac acc gtt gaa cgt cgg ctg   3642
Leu Thr Asn Phe Val Ile Cys Met Gly Asn Thr Val Glu Arg Arg Leu
1105               1110                1115                1120

ggt gtt gtt cat aat ccc ttt aaa agg tct ggg gat ggc cat gac ctc   3690
Gly Val Val His Asn Pro Phe Lys Arg Ser Gly Asp Gly His Asp Leu
               1125                1130                1135

agg gcg gta gcg tgaccaaagt tcatatccat accaattatt tttatttaaa       3742
Arg Ala Val Ala
           1140

atatcaactt attcgagttg ttttatttag ttcaaagaag gtatcaaa ttg ata gtt  3799
                                                    Leu Ile Val

ata gat ttt ttt tgt ggc tgt ggt gga gcc agt gaa ggg cta cgt cag   3847
Ile Asp Phe Phe Cys Gly Cys Gly Gly Ala Ser Glu Gly Leu Arg Gln
   1145                1150                1155

gct ggc ttt gat atc gag ctt gga tta gat att gac caa caa gca tca   3895
Ala Gly Phe Asp Ile Glu Leu Gly Leu Asp Ile Asp Gln Gln Ala Ser
1160               1165                1170                1175

gaa aca ttt aaa gct aat ttc cct gat gca aaa ttc atc caa gat gat   3943
Glu Thr Phe Lys Ala Asn Phe Pro Asp Ala Lys Phe Ile Gln Asp Asp
               1180                1185                1190

att agg aaa atc gaa cct caa gat atc tcc gac atc att gat att aaa   3991
Ile Arg Lys Ile Glu Pro Gln Asp Ile Ser Asp Ile Ile Asp Ile Lys
           1195                1200                1205

gct aaa cgg cct ttg tta ctg agt gca tgt gca cca tgt caa cca ttt   4039
Ala Lys Arg Pro Leu Leu Leu Ser Ala Cys Ala Pro Cys Gln Pro Phe
       1210                1215                1220

tcg caa cag aat aaa aat aaa act agt gac gac tca agg aga aat cta   4087
Ser Gln Gln Asn Lys Asn Lys Thr Ser Asp Asp Ser Arg Arg Asn Leu
   1225                1230                1235

cta aat gaa act cat cgt ttt att aga gaa ctt ctt cct gaa tat att   4135
Leu Asn Glu Thr His Arg Phe Ile Arg Glu Leu Leu Pro Glu Tyr Ile
1240               1245                1250                1255
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atg ctt gaa aat gtt cct gga atg caa aaa att gat gaa gaa aaa gaa   4183
Met Leu Glu Asn Val Pro Gly Met Gln Lys Ile Asp Glu Glu Lys Glu
               1260                1265                1270

ggc cca ttt cag gag ttt att aag cta ctt aaa gag tta gag tat aac   4231
Gly Pro Phe Gln Glu Phe Ile Lys Leu Leu Lys Glu Leu Glu Tyr Asn
           1275                1280                1285

tat ata tct ttt ata gcc aat gct gag aac tat ggg att ccc caa aga   4279
Tyr Ile Ser Phe Ile Ala Asn Ala Glu Asn Tyr Gly Ile Pro Gln Arg
       1290                1295                1300

aga aaa aga ctc gtg ctc tta gct agt cga gta ggt aaa gtt acc cta   4327
Arg Lys Arg Leu Val Leu Leu Ala Ser Arg Val Gly Lys Val Thr Leu
   1305                1310                1315

cca gag ata acc cat ggt aaa aat aaa atc cca ttc aaa act gta cga   4375
Pro Glu Ile Thr His Gly Lys Asn Lys Ile Pro Phe Lys Thr Val Arg
1320                1325                1330                1335

gat tat atc cag gac ttc aca aag tta tgt tca gga gaa acc gac ccc   4423
Asp Tyr Ile Gln Asp Phe Thr Lys Leu Cys Ser Gly Glu Thr Asp Pro
               1340                1345                1350

aaa gat cct tta cat agg gct gga aca ctg agc cct ctt aac cta aaa   4471
Lys Asp Pro Leu His Arg Ala Gly Thr Leu Ser Pro Leu Asn Leu Lys
           1355                1360                1365

aga att atg cac act cca gaa gga ggg gat aga aga aat tgg cca gaa   4519
Arg Ile Met His Thr Pro Glu Gly Gly Asp Arg Arg Asn Trp Pro Glu
       1370                1375                1380

gag tta gtt aat aaa tgc cat aaa aat tat gat ggc cac aca gat act   4567
Glu Leu Val Asn Lys Cys His Lys Asn Tyr Asp Gly His Thr Asp Thr
   1385                1390                1395

tat gga aga atg agt tgg gat aag cct gcg cct aca ctt acg acg aaa   4615
Tyr Gly Arg Met Ser Trp Asp Lys Pro Ala Pro Thr Leu Thr Thr Lys
1400                1405                1410                1415

tgt aat agt tac tcc aat ggt cgt ttt ggg cat cct gac ccc act caa   4663
Cys Asn Ser Tyr Ser Asn Gly Arg Phe Gly His Pro Asp Pro Thr Gln
               1420                1425                1430

cat aga gca att agc ata aga gaa gca tca aga tta caa aca ttt cct   4711
His Arg Ala Ile Ser Ile Arg Glu Ala Ser Arg Leu Gln Thr Phe Pro
           1435                1440                1445
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tta agc tat gtt ttt aaa ggt tcg ctg aat tca atg gca aag caa atc   4759
Leu Ser Tyr Val Phe Lys Gly Ser Leu Asn Ser Met Ala Lys Gln Ile
       1450                1455                1460

ggc aat gct gta cct tgc gaa ctc gct aga cta ttt ggg cta cat ctc   4807
Gly Asn Ala Val Pro Cys Glu Leu Ala Arg Leu Phe Gly Leu His Leu
   1465                1470                1475

ata gaa aat tgt act aat aag gat tca tagatatatg gctaaaataa         4854
Ile Glu Asn Cys Thr Asn Lys Asp Ser
1480                1485

gaacaaaggc tcgagctttg gac atg ctt ggc aga caa caa att gca ggt ata 4907
                         Met Leu Gly Arg Gln Gln Ile Ala Gly Ile
                            1490                1495

cct act gcc ttg agt gag tta ttt aaa aat gct cat gat gcc tat gct   4955
Pro Thr Ala Leu Ser Glu Leu Phe Lys Asn Ala His Asp Ala Tyr Ala
   1500                1505                1510

gat aat gtc gaa gtt gat ttt ttt agg aaa gaa aat ctt ctt atc ttg   5003
Asp Asn Val Glu Val Asp Phe Phe Arg Lys Glu Asn Leu Leu Ile Leu
1515                1520                1525                1530

aga gat gat gga tta ggt atg aca acc gat gaa ttt gaa gag agg tgg   5051
Arg Asp Asp Gly Leu Gly Met Thr Thr Asp Glu Phe Glu Glu Arg Trp
               1535                1540                1545

ttg act att gga acc tcc agc aaa tta atc gac gat gat gca att aat   5099
Leu Thr Ile Gly Thr Ser Ser Lys Leu Ile Asp Asp Asp Ala Ile Asn
           1550                1555                1560

aaa cca gca gtg gat agt aat aaa gcc ttt cgc cct atc atg gga gag   5147
Lys Pro Ala Val Asp Ser Asn Lys Ala Phe Arg Pro Ile Met Gly Glu
       1565                1570                1575

aaa gga ata ggc cgt tta tct atc gca gca att gga cca cag gtg ctg   5195
Lys Gly Ile Gly Arg Leu Ser Ile Ala Ala Ile Gly Pro Gln Val Leu
   1580                1585                1590

gtt ctt act agg gcc aaa aga gac aat gag ctt aag cca tta gtt gct   5243
Val Leu Thr Arg Ala Lys Arg Asp Asn Glu Leu Lys Pro Leu Val Ala
1595                1600                1605                1610

gca ttt gtt aat tgg agt tta ttt gct ata cca tca ctt gat ctt gat   5291
Ala Phe Val Asn Trp Ser Leu Phe Ala Ile Pro Ser Leu Asp Leu Asp
               1615                1620                1625
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gat ata gaa ata cca att aga act att atc aac gac gaa tgc ttc act   5339
Asp Ile Glu Ile Pro Ile Arg Thr Ile Ile Asn Asp Glu Cys Phe Thr
          1630                1635                1640

aaa aaa act ctt gat gag atg att gag caa gca aga aat aat tta gac   5387
Lys Lys Thr Leu Asp Glu Met Ile Glu Gln Ala Arg Asn Asn Leu Asp
      1645                1650                1655

tct tta tca cac aaa ata tca aaa tca aaa gta tca caa ata aat aca   5435
Ser Leu Ser His Lys Ile Ser Lys Ser Lys Val Ser Gln Ile Asn Thr
   1660                1665                1670

caa tta tca tct ttt gaa ttt gat cct att cta tgg gaa aaa aaa tta   5483
Gln Leu Ser Ser Phe Glu Phe Asp Pro Ile Leu Trp Glu Lys Lys Leu
1675                1680                1685                1690

ggt ggg cta aga cta tct gga gat ggg cat gga act cac ttc ata ata   5531
Gly Gly Leu Arg Leu Ser Gly Asp Gly His Gly Thr His Phe Ile Ile
               1695                1700                1705

atg cct acc gaa gaa ata tta ata gat gac att tcc acg agc gat agc   5579
Met Pro Thr Glu Glu Ile Leu Ile Asp Asp Ile Ser Thr Ser Asp Ser
          1710                1715                1720

aat aaa aca tca gag cag tct tct cgc tta gaa aaa gct tta tta ggt   5627
Asn Lys Thr Ser Glu Gln Ser Ser Arg Leu Glu Lys Ala Leu Leu Gly
      1725                1730                1735

ttt aca aac aca atg tac agt gat tca aac cct cct att ata gct cgt   5675
Phe Thr Asn Thr Met Tyr Ser Asp Ser Asn Pro Pro Ile Ile Ala Arg
   1740                1745                1750

ttt aga gac tat ctg gaa gat ggt gag tgc att gac aga att agc gaa   5723
Phe Arg Asp Tyr Leu Glu Asp Gly Glu Cys Ile Asp Arg Ile Ser Glu
1755                1760                1765                1770

tca att ttt ttt aca ccg caa gaa ttc aat ctt gca gat cac cac att   5771
Ser Ile Phe Phe Thr Pro Gln Glu Phe Asn Leu Ala Asp His His Ile
               1775                1780                1785

gaa gga tgg ttc aat gaa ttt ggt caa ttc agt gga act gtt tct gtt   5819
Glu Gly Trp Phe Asn Glu Phe Gly Gln Phe Ser Gly Thr Val Ser Val
          1790                1795                1800

tat ggt gaa gag cca att cat cat gtc gtg act tgg aaa aat aat aat   5867
Tyr Gly Glu Glu Pro Ile His His Val Val Thr Trp Lys Asn Asn Asn
      1805                1810                1815
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caa tta acc caa tgc ggt cca ttt aaa ata aaa tta gcg tat att cat   5915
Gln Leu Thr Gln Cys Gly Pro Phe Lys Ile Lys Leu Ala Tyr Ile His
   1820                1825                1830

ggt cgg ctt cgt gat tca cgc tta ccc atg gag ttg tgg gcc cct ctg   5963
Gly Arg Leu Arg Asp Ser Arg Leu Pro Met Glu Leu Trp Ala Pro Leu
1835                1840                1845                1850

aag gag aaa aca gat aga tat ggt ggt tta tat atc tat cga gat gga   6011
Lys Glu Lys Thr Asp Arg Tyr Gly Gly Leu Tyr Ile Tyr Arg Asp Gly
               1855                1860                1865

tta aga att ttg ccc tat gga gat tca gat acg gat ttt cta aaa ata   6059
Leu Arg Ile Leu Pro Tyr Gly Asp Ser Asp Thr Asp Phe Leu Lys Ile
           1870                1875                1880

gaa aag aga aga acg tta tcc gct tct gaa tat ttt ttc tca tat cga   6107
Glu Lys Arg Arg Thr Leu Ser Ala Ser Glu Tyr Phe Phe Ser Tyr Arg
       1885                1890                1895

cgt ttg ttt gga gca ata gaa tta aca aaa gaa aac aat gct tca tta   6155
Arg Leu Phe Gly Ala Ile Glu Leu Thr Lys Glu Asn Asn Ala Ser Leu
   1900                1905                1910

gtt gaa aaa gct ggg cga gaa gga ttc att gaa aat aag cca tat aaa   6203
Val Glu Lys Ala Gly Arg Glu Gly Phe Ile Glu Asn Lys Pro Tyr Lys
1915                1920                1925                1930

cag ttt aaa gaa atg ctt gaa aat ttc ttc atc gaa atc gca aga gat   6251
Gln Phe Lys Glu Met Leu Glu Asn Phe Phe Ile Glu Ile Ala Arg Asp
               1935                1940                1945

ttc ttt aag gac gat ggc gat atg tct gaa tta ttt gtt gag aca aag   6299
Phe Phe Lys Asp Asp Gly Asp Met Ser Glu Leu Phe Val Glu Thr Lys
           1950                1955                1960

caa cgt aga aat gaa gaa cat gat ttg tta tct aaa aga tct aaa caa   6347
Gln Arg Arg Asn Glu Glu His Asp Leu Leu Ser Lys Arg Ser Lys Gln
       1965                1970                1975

act aaa gct aaa aaa gat aga tta aag aaa gat ctg tat gat ttt ttt   6395
Thr Lys Ala Lys Lys Asp Arg Leu Lys Lys Asp Leu Tyr Asp Phe Phe
   1980                1985                1990

gat aag tta gat aat gat tac tgg aat att gaa ata aat aag cta atc   6443
Asp Lys Leu Asp Asn Asp Tyr Trp Asn Ile Glu Ile Asn Lys Leu Ile
1995                2000                2005                2010
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aat aaa aac gag gaa tat ttc tcc agt aca gaa ata aca gac acc aat   6491
Asn Lys Asn Glu Glu Tyr Phe Ser Ser Thr Glu Ile Thr Asp Thr Asn
                2015                2020                2025

ata gat tat gta tac aat aaa att aaa gaa caa aat gat gct atc att   6539
Ile Asp Tyr Val Tyr Asn Lys Ile Lys Glu Gln Asn Asp Ala Ile Ile
            2030                2035                2040

aaa aat cta cgt aat tct gtg gat ata aag aaa ccc tct gga gtt gga   6587
Lys Asn Leu Arg Asn Ser Val Asp Ile Lys Lys Pro Ser Gly Val Gly
        2045                2050                2055

tta aca aaa gag tta tct aat tta tgg gat aga tat caa ata gaa aga   6635
Leu Thr Lys Glu Leu Ser Asn Leu Trp Asp Arg Tyr Gln Ile Glu Arg
    2060                2065                2070

caa aaa ata ctg tta tca cta aat gag cta aaa gat aac gtt gat aga   6683
Gln Lys Ile Leu Leu Ser Leu Asn Glu Leu Lys Asp Asn Val Asp Arg
2075                2080                2085                2090

aag ctt ata gaa ctg gat aat aaa aat aat gat ttt ctc aac tta cgg   6731
Lys Leu Ile Glu Leu Asp Asn Lys Asn Asn Asp Phe Leu Asn Leu Arg
                2095                2100                2105

aag aga ctt gaa gat tct ttg aat cta caa caa agt tac tat gaa aaa   6779
Lys Arg Leu Glu Asp Ser Leu Asn Leu Gln Gln Ser Tyr Tyr Glu Lys
            2110                2115                2120

gaa cta aca aag tta tat aat gac gct aaa aat gct ttg aaa gat gtg   6827
Glu Leu Thr Lys Leu Tyr Asn Asp Ala Lys Asn Ala Leu Lys Asp Val
        2125                2130                2135

caa tct aaa gca aat agg tta att tct gat aat aag aaa aaa cat aag   6875
Gln Ser Lys Ala Asn Arg Leu Ile Ser Asp Asn Lys Lys Lys His Lys
    2140                2145                2150

agt gaa cta aaa aac att tct tat gaa ttc caa tca act aat ctc aat   6923
Ser Glu Leu Lys Asn Ile Ser Tyr Glu Phe Gln Ser Thr Asn Leu Asn
2155                2160                2165                2170

ggc aaa gat act gcg tat ata ttg gat gta aaa aga aat cta gaa agt   6971
Gly Lys Asp Thr Ala Tyr Ile Leu Asp Val Lys Arg Asn Leu Glu Ser
                2175                2180                2185

aaa att gag aat act tca aac gaa gtg att aat gaa ata aga aaa cta   7019
Lys Ile Glu Asn Thr Ser Asn Glu Val Ile Asn Glu Ile Arg Lys Leu
            2190                2195                2200
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acc gac cag att gca ata att agt gat agt acc act tct gaa aat tta   7067
Thr Asp Gln Ile Ala Ile Ile Ser Asp Ser Thr Thr Ser Glu Asn Leu
       2205                2210                2215

tca tcg gct caa gta act gaa gca atc gaa act gaa ctt gaa cat tta   7115
Ser Ser Ala Gln Val Thr Glu Ala Ile Glu Thr Glu Leu Glu His Leu
   2220                2225                2230

cga gac caa caa gca aat aac gca gag tta ata cta ctt ggc atg gct   7163
Arg Asp Gln Gln Ala Asn Asn Ala Glu Leu Ile Leu Leu Gly Met Ala
2235                2240                2245                2250

ctt tct gta gta cat cat gaa ttt aat ggt aat att agg gca att aga   7211
Leu Ser Val Val His His Glu Phe Asn Gly Asn Ile Arg Ala Ile Arg
               2255                2260                2265

agt gcg cta agg gaa tta aaa gca tgg gct gac aga aat cct aag ctt   7259
Ser Ala Leu Arg Glu Leu Lys Ala Trp Ala Asp Arg Asn Pro Lys Leu
           2270                2275                2280

gat att ata tac caa aaa atc aga act agt ttt gat cac tta gat ggt   7307
Asp Ile Ile Tyr Gln Lys Ile Arg Thr Ser Phe Asp His Leu Asp Gly
       2285                2290                2295

tat tta aaa acc ttt aca cca ttg aca aga cgt tta agt cgc tct aaa   7355
Tyr Leu Lys Thr Phe Thr Pro Leu Thr Arg Arg Leu Ser Arg Ser Lys
   2300                2305                2310

acc aat ata act gga act gcc att tta gaa ttt atc aga gat gta ttc   7403
Thr Asn Ile Thr Gly Thr Ala Ile Leu Glu Phe Ile Arg Asp Val Phe
2315                2320                2325                2330

gat gat cgt ctt gag aaa gaa gga att gaa tta ttc act acc tca aag   7451
Asp Asp Arg Leu Glu Lys Glu Gly Ile Glu Leu Phe Thr Thr Ser Lys
               2335                2340                2345

ttt gtt aat caa gaa att gta act tac aca tca acc att tac cct gtc   7499
Phe Val Asn Gln Glu Ile Val Thr Tyr Thr Ser Thr Ile Tyr Pro Val
           2350                2355                2360

ttt ata aat cta att gat aac gca ata tac tgg ctt ggg aaa aca act   7547
Phe Ile Asn Leu Ile Asp Asn Ala Ile Tyr Trp Leu Gly Lys Thr Thr
       2365                2370                2375

gga gaa aaa aga ctt ata ctt gat gct act gaa aca gga ttt gtt att   7595
Gly Glu Lys Arg Leu Ile Leu Asp Ala Thr Glu Thr Gly Phe Val Ile
   2380                2385                2390
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ggt gat act ggt ccc ggt gtt tca act aga gat cga gat ata ata ttt   7643
Gly Asp Thr Gly Pro Gly Val Ser Thr Arg Asp Arg Asp Ile Ile Phe
2395                2400                2405                2410

gat atg gga ttt aca cga aaa aca gga ggg cgt gga atg gga tta ttc   7691
Asp Met Gly Phe Thr Arg Lys Thr Gly Gly Arg Gly Met Gly Leu Phe
                2415                2420                2425

att tcc aaa gag tgt tta tct cga gat gga ttt act ata aga ttg gat   7739
Ile Ser Lys Glu Cys Leu Ser Arg Asp Gly Phe Thr Ile Arg Leu Asp
            2430                2435                2440

gat tac act cct gaa cag ggt gct ttc ttt att att gag cca tca gaa   7787
Asp Tyr Thr Pro Glu Gln Gly Ala Phe Phe Ile Ile Glu Pro Ser Glu
        2445                2450                2455

gaa aca agt gaa tag cggatataaa taa atg aca agc tct act gat ttt    7836
Glu Thr Ser Glu                     Met Thr Ser Ser Thr Asp Phe
    2460                                2465                2470

cat aaa ctt tct gaa gac tgc gtt cgc cgt ttt tta cat tct gta gtt   7884
His Lys Leu Ser Glu Asp Cys Val Arg Arg Phe Leu His Ser Val Val
                2475                2480                2485

gct gta gat gac aat atg tct ttt gga gct ggt agt gat act ttc cct   7932
Ala Val Asp Asp Asn Met Ser Phe Gly Ala Gly Ser Asp Thr Phe Pro
            2490                2495                2500

aca gac gaa gat att aat gct tta gtt gat ccc gac gat gat cct aca   7980
Thr Asp Glu Asp Ile Asn Ala Leu Val Asp Pro Asp Asp Asp Pro Thr
        2505                2510                2515

cca ata ata aca gca tca gca tcc cca agg ata gaa tca act aaa tca   8028
Pro Ile Ile Thr Ala Ser Ala Ser Pro Arg Ile Glu Ser Thr Lys Ser
    2520                2525                2530

aaa gca aag gta aaa aac cat cct ttt gat tac caa gct cta gca gaa   8076
Lys Ala Lys Val Lys Asn His Pro Phe Asp Tyr Gln Ala Leu Ala Glu
2535                2540                2545                2550

gct ttc gcc aaa gat ggt att gct tgt tgc gga tta tta gct aag agt   8124
Ala Phe Ala Lys Asp Gly Ile Ala Cys Cys Gly Leu Leu Ala Lys Ser
                2555                2560                2565

ttt aat gtt gaa gaa aga gat ata att aca gca tca tcc cac aag gca   8172
Phe Asn Val Glu Glu Arg Asp Ile Ile Thr Ala Ser Ser His Lys Ala
            2570                2575                2580
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gat ata aca ata ctt gac tgg gat atg caa agc gat agt ggg caa ttt   8220
Asp Ile Thr Ile Leu Asp Trp Asp Met Gln Ser Asp Ser Gly Gln Phe
       2585                2590                2595

gct att gaa ata ata aaa tcg ata atc gtt tca gat ata aat tct gga   8268
Ala Ile Glu Ile Ile Lys Ser Ile Ile Val Ser Asp Ile Asn Ser Gly
   2600                2605                2610

gga cgt tta cgt ctt ctt tct att tat act ggt gaa cat gtt act gct   8316
Gly Arg Leu Arg Leu Leu Ser Ile Tyr Thr Gly Glu His Val Thr Ala
2615                2620                2625                2630

gtt ata act aag ttg aac aat gag tta aag aaa aca tac cgt agc gta   8364
Val Ile Thr Lys Leu Asn Asn Glu Leu Lys Lys Thr Tyr Arg Ser Val
               2635                2640                2645

ata aaa aat gat gat agt att ttt att gaa gat aac tat gca ctc gaa   8412
Ile Lys Asn Asp Asp Ser Ile Phe Ile Glu Asp Asn Tyr Ala Leu Glu
           2650                2655                2660

caa tgg tgt ata gtt gtt att agt aaa gac gtt tat gaa aaa gat ctt   8460
Gln Trp Cys Ile Val Val Ile Ser Lys Asp Val Tyr Glu Lys Asp Leu
       2665                2670                2675

cca aat gtg tta ata aaa aaa ttc act aac ctt aca gct ggg ttg cta   8508
Pro Asn Val Leu Ile Lys Lys Phe Thr Asn Leu Thr Ala Gly Leu Leu
   2680                2685                2690

tcc aac gcc gca ctc tct tgc att tct gaa ata aga gaa aaa acc cat   8556
Ser Asn Ala Ala Leu Ser Cys Ile Ser Glu Ile Arg Glu Lys Thr His
2695                2700                2705                2710

ggg ata tta aca aaa tat aat aat aaa tta gac act gca tat gtt tcc   8604
Gly Ile Leu Thr Lys Tyr Asn Asn Lys Leu Asp Thr Ala Tyr Val Ser
               2715                2720                2725

cac atc tta aat tta ata aaa tcc aag gag tca agg gca tat gct tat   8652
His Ile Leu Asn Leu Ile Lys Ser Lys Glu Ser Arg Ala Tyr Ala Tyr
           2730                2735                2740

gaa aat gct cat gat tat gca gta gat tta att tct gaa gaa ata aga   8700
Glu Asn Ala His Asp Tyr Ala Val Asp Leu Ile Ser Glu Glu Ile Arg
       2745                2750                2755

tca ata ttg caa ata agt gaa aac tta aag aaa tct cta agc aaa aac   8748
Ser Ile Leu Gln Ile Ser Glu Asn Leu Lys Lys Ser Leu Ser Lys Asn
   2760                2765                2770
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tcc tta tcc cat tgg cct att ttt cac tat gca aaa aat ggt tgt aag   8796
Ser Leu Ser His Trp Pro Ile Phe His Tyr Ala Lys Asn Gly Cys Lys
2775                2780                2785                2790

aat ttt cta tta act gga aaa aaa caa aaa gac tta tca gta gaa cat   8844
Asn Phe Leu Leu Thr Gly Lys Lys Gln Lys Asp Leu Ser Val Glu His
                2795                2800                2805

cta agg aat ata ctc tct gct gat tct tta gaa gaa att caa cac gct   8892
Leu Arg Asn Ile Leu Ser Ala Asp Ser Leu Glu Glu Ile Gln His Ala
            2810                2815                2820

att gaa cac gca tct tta ggt aaa aag gaa tac tta agc caa gat ggt   8940
Ile Glu His Ala Ser Leu Gly Lys Lys Glu Tyr Leu Ser Gln Asp Gly
        2825                2830                2835

gaa gaa gat aaa aag tta atg caa tta tgc tct ctg gaa atc acg cgc   8988
Glu Glu Asp Lys Lys Leu Met Gln Leu Cys Ser Leu Glu Ile Thr Arg
    2840                2845                2850

agg agt tta aga tat cat tct cat ata gat aat gtg tcc tta aaa caa   9036
Arg Ser Leu Arg Tyr His Ser His Ile Asp Asn Val Ser Leu Lys Gln
2855                2860                2865                2870

gga act tta ctt tta gat gca tat aat ttt gtc tat cta tgc ata caa   9084
Gly Thr Leu Leu Leu Asp Ala Tyr Asn Phe Val Tyr Leu Cys Ile Gln
                2875                2880                2885

cca tta tgt gat agc gtc aga ttg cat gaa aaa gcc gat ttt tta ttc   9132
Pro Leu Cys Asp Ser Val Arg Leu His Glu Lys Ala Asp Phe Leu Phe
            2890                2895                2900

ctc agg gga aca ctg gac gat aat aat tac aat ttg tta atc gaa gat   9180
Leu Arg Gly Thr Leu Asp Asp Asn Asn Tyr Asn Leu Leu Ile Glu Asp
        2905                2910                2915

gaa tat ggc ggt ttt tat aaa att aaa atg ccg gca aaa gct tct aat   9228
Glu Tyr Gly Gly Phe Tyr Lys Ile Lys Met Pro Ala Lys Ala Ser Asn
    2920                2925                2930

att att tca ttt tca ttt gga gtc gaa aat gga aac ggt gtc atc ata   9276
Ile Ile Ser Phe Ser Phe Gly Val Glu Asn Gly Asn Gly Val Ile Ile
2935                2940                2945                2950

ggg aaa aag aac aat cta gtt aat act gac tat atc tca ttc gtt cct   9324
Gly Lys Lys Asn Asn Leu Val Asn Thr Asp Tyr Ile Ser Phe Val Pro
                2955                2960                2965
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tta ctc gtt gaa aaa ata tct act cca aaa gta ttg aaa tgg atc ggg   9372
Leu Leu Val Glu Lys Ile Ser Thr Pro Lys Val Leu Lys Trp Ile Gly
          2970                2975                2980

gaa ata aaa aca acg tac gcg caa aaa ata aca act gat att gtt gct   9420
Glu Ile Lys Thr Thr Tyr Ala Gln Lys Ile Thr Thr Asp Ile Val Ala
       2985                2990                2995

aat ctg tca aga ata ggt tta gat caa cat gag tgg tta cga ata aaa   9468
Asn Leu Ser Arg Ile Gly Leu Asp Gln His Glu Trp Leu Arg Ile Lys
   3000                3005                3010

tca aaa gat ata taaatgatta tatatgccgt cgttttataa aaactggcgg       9520
Ser Lys Asp Ile
3015

catgtatatc tagttagtcc atcatagaag tcaagaaatt tagtttgccc tatatcttat 9580

agaaaatata ttttatatgc ttaaaaaaca ccatctttct aagatggcat ttatgtgctt 9640

tgtttcgatc aattacaact gatatattac catattgatt aattttatgt tatttaccaa 9700

agtaacggca tcttaatata tcgtcataat atagtgcgcg ttctgactct aatactgaaa 9760

aatttatttg ttctatttta cacttactgc aaatagcatc cagtttatca tatagtgtcg 9820

catcaattgg cgcag atg tca tca cgc caa atc ctt gag cat tat aat gct  9871
                Met Ser Ser Arg Gln Ile Leu Glu His Tyr Asn Ala
                   3020                3025                3030

cta aca tat ccc cta cat caa tca atc ttg ttg cag ata atg act tcg   9919
Leu Thr Tyr Pro Leu His Gln Ser Ile Leu Leu Gln Ile Met Thr Ser
              3035                3040                3045

aat ttg tta tca gtt tgc act gga aaa tcc att tac gag gat atc tcc   9967
Asn Leu Leu Ser Val Cys Thr Gly Lys Ser Ile Tyr Glu Asp Ile Ser
          3050                3055                3060

ggc agt tct tgg aat atc ata cac ttc aat atc cct ctc ccc atc tct   10015
Gly Ser Ser Trp Asn Ile Ile His Phe Asn Ile Pro Leu Pro Ile Ser
       3065                3070                3075

aga gcg aga ctt tcc ata ttt tct tat tgt gtc aga att aaa cct tgg   10063
Arg Ala Arg Leu Ser Ile Phe Ser Tyr Cys Val Arg Ile Lys Pro Trp
   3080                3085                3090

atg agt atg gat tac atg taaccggctc atttaaaccg tctggtctgt          10111
Met Ser Met Asp Tyr Met
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3095                3100

ttcctccggt tttacaaaaa ta atg tcc atc att ttt aat gga cac tat cgt  10163
                        Met Ser Ile Ile Phe Asn Gly His Tyr Arg
                                              3105                3110

atg aaa cac cgg act tgg atc act gaa gct tta cgt ctt cac ttt gaa   10211
Met Lys His Arg Thr Trp Ile Thr Glu Ala Leu Arg Leu His Phe Glu
                3115                3120                3125

gaa cat tta ccc cag gtt gtg gtc ggg cgt cgc ctg ggc gta cca aaa   10259
Glu His Leu Pro Gln Val Val Val Gly Arg Arg Leu Gly Val Pro Lys
            3130                3135                3140

tca aca gct tgt ggt atg ttc gtg cgc ttt cgc aaa gct ggc ttt tca   10307
Ser Thr Ala Cys Gly Met Phe Val Arg Phe Arg Lys Ala Gly Phe Ser
        3145                3150                3155

tgg cct ctg ccc gca ggt atg tcg gag cgg gag ctt gat ggc cgt ctt   10355
Trp Pro Leu Pro Ala Gly Met Ser Glu Arg Glu Leu Asp Gly Arg Leu
    3160                3165                3170

tac ggg agt acc tcc aca gta cct gtc gta ctt tgt agt gga tcg gta   10403
Tyr Gly Ser Thr Ser Thr Val Pro Val Val Leu Cys Ser Gly Ser Val
3175                3180                3185                3190

att cag gac acc tcg aaa tcc tgt taatgttaaa acagtgaaaa tgaggtgatg  10457
Ile Gln Asp Thr Ser Lys Ser Cys
                3195

c atg atc aaa act cgt cgg act aaa cgt acc ttt tcc ccg gag ttc aag 10506
  Met Ile Lys Thr Arg Arg Thr Lys Arg Thr Phe Ser Pro Glu Phe Lys
     3200                3205                3210

ctt gaa gct ttc gag cag gtg gtg gtt aaa tac cag cgt gat gtc aga   10554
Leu Glu Ala Phe Glu Gln Val Val Val Lys Tyr Gln Arg Asp Val Arg
3215                3220                3225                3230

gaa gtc gcg cag gca ctc gag ctc aac cct gac cat ttg cgt aaa tgg   10602
Glu Val Ala Gln Ala Leu Glu Leu Asn Pro Asp His Leu Arg Lys Trp
                3235                3240                3245

ata cgg ttg tat aag cag gaa ctt cag ggt att gag cca gct ggt aat   10650
Ile Arg Leu Tyr Lys Gln Glu Leu Gln Gly Ile Glu Pro Ala Gly Asn
            3250                3255                3260

gct att acc cct gaa caa cgc gaa att cag cag ctt aaa gcg cag ata   10698
Ala Ile Thr Pro Glu Gln Arg Glu Ile Gln Gln Leu Lys Ala Gln Ile
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      3265                3270                3275

aag cgc gtt gag atg gaa aaa gaa ata cta aag cag gct gcc gtg ctg   10746
Lys Arg Val Glu Met Glu Lys Glu Ile Leu Lys Gln Ala Ala Val Leu
   3280                3285                3290

atg agc gaa atc ccc ggg aag ctg tcg cgc taatcacaca gctgaaagca     10796
Met Ser Glu Ile Pro Gly Lys Leu Ser Arg
3295                3300

aagtggccag tgtgggttat ttgtcattta ttcggtatta accgtagcgt ttattacgcg 10856

caggtgaagc gtcctgttaa tgtgcaaaga attgaattac gaagccgggt gagggctttc 10916

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tggcgttgat gcaggccggt ggctggcatg acgactgatg cgggaatgag ggctgacaag 11036

tcgacagccg gttaaacatc acaaccgggt aaacgaagac aaaagtccgc cattgccaaa 11096

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             20                  25                  30

Glu Leu Ala Asn Ile Ile Gly His His Ala Gly Ile Asp Asp Asn Thr
         35                  40                  45

Ala Ala Lys Ala Ile Ala His Ala Ile Leu Gly Gly Val Thr Ala Ala
     50                  55                  60

Leu Gln Gly Asn Ser Ala Ala Ala Gly Ala Ile Gly Ala Gly Thr Gly
 65                  70                  75                  80

Glu Val Ile Ala Ser Ala Ile Ala Lys Ser Leu Tyr Pro Gly Val Asp
                 85                  90                  95
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Pro Ser Lys Leu Thr Glu Asp Gln Lys Gln Thr Val Ser Thr Leu Ala
            100                 105                 110

Thr Leu Ser Ala Gly Met Ala Gly Gly Ile Ala Ser Gly Asp Val Ala
        115                 120                 125

Gly Ala Ala Ala Gly Ala Gly Ala Gly Lys Asn Val Val Glu Asn Asn
    130                 135                 140

Ala Leu Ser Leu Val Ala Arg Gly Cys Ala Val Ala Ala Pro Cys Arg
145                 150                 155                 160

Thr Lys Val Ala Glu Gln Leu Leu Glu Ile Gly Ala Lys Ala Gly Met
                165                 170                 175

Ala Gly Leu Ala Gly Ala Ala Val Lys Asp Met Ala Asp Arg Met Thr
            180                 185                 190

Ser Asp Glu Leu Glu His Leu Ile Thr Leu Gln Met Met Gly Asn Asp
        195                 200                 205

Glu Ile Thr Thr Lys Tyr Leu Ser Ser Leu His Asp Lys Tyr Gly Ser
    210                 215                 220

Gly Ala Ala Ser Asn Pro Asn Ile Gly Lys Asp Leu Thr Asp Ala Glu
225                 230                 235                 240

Lys Val Glu Leu Gly Gly Ser Gly Ser Gly Thr Gly Thr Pro Pro Pro
                245                 250                 255

Ser Glu Asn Asp Pro Lys Gln Gln Asn Glu Lys Thr Val Asp Lys Leu
            260                 265                 270

Asn Gln Lys Gln Glu Ser Ala Ile Lys Lys Ile Asp Asn Thr Ile Lys
        275                 280                 285

Asn Ala Leu Lys Asp His Asp Ile Ile Gly Thr Leu Lys Asp Met Asp
    290                 295                 300

Gly Lys Pro Val Pro Lys Glu Asn Gly Gly Tyr Trp Asp His Met Gln
305                 310                 315                 320

Glu Met Gln Asn Thr Leu Arg Gly Leu Arg Asn His Ala Asp Thr Leu
                325                 330                 335

Lys Asn Val Asn Asn Pro Glu Ala Gln Ala Ala Tyr Gly Arg Ala Thr
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Met Ile Thr Leu Arg Lys Leu Ile Gly Asn Ile Asn Met Thr Lys Glu
  1               5                  10                  15

Pro Glu Gln Gln Ser Pro Leu Glu Leu Trp Phe Glu Arg Ile Ile Asp
             20                  25                  30

Val Pro Leu Glu Lys Leu Thr Val Glu Asp Leu Cys Arg Ala Ile Arg
         35                  40                  45

Gln Asn Leu Cys Ile Asp Gln Leu Met Pro Arg Val Leu Glu Val Leu
     50                  55                  60

Thr Lys Glu Pro Leu Ala Gly Glu Tyr Tyr Asp Gly Glu Leu Ile Ala
 65                  70                  75                  80

Ala Leu Ser Thr Ile Lys Gly Glu Asp Leu Lys Asp Gln Lys Ser Thr
                 85                  90                  95

Phe Thr Gln Ile Arg Gln Leu Ile Asn Gln Leu Glu Pro Ser Asp Ile
            100                 105                 110

Asn Asp Asp Leu Arg Lys Asp Ile Leu Lys Ile Asn Gln Ile Ile Val
        115                 120                 125
```

<210> 37
<211> 107
<212> PRT
<213> Escherichia coli

<400> 37

```
Met Val Ala Lys Ala Phe Ala Tyr Ala Leu Asn Gln Trp Pro Ala Leu
  1               5                  10                  15

Thr Tyr Tyr Ala Asn Asp Gly Trp Val Glu Ile Asp Asn Asn Ile Ala
             20                  25                  30
```

Glu Asn Ala Leu Arg Ala Val Ser Leu Gly Arg Lys Asn Phe Leu Phe
35 40 45

Phe Gly Ser Asp His Gly Gly Glu Arg Gly Ala Leu Leu Tyr Ser Leu
50 55 60

Ile Gly Thr Cys Lys Leu Asn Asp Val Asp Pro Glu Ser Tyr Leu Arg
65 70 75 80

His Val Leu Ala Val Ile Ala Asp Trp Pro Val Asn Arg Val Ser Glu
85 90 95

Leu Leu Pro Trp Arg Ile Ala Leu Pro Ala Glu
100 105

<210> 38
<211> 86
<212> PRT
<213> Escherichia coli

<400> 38
Met Leu Met Ser Val Gln Lys Glu Lys Asn Val Ala Glu Ser Val Val
1 5 10 15

Ser Glu Thr His Thr Gly Asp Ser Val Tyr Ala Ser Leu Phe Glu Lys
20 25 30

Ile Asn Leu Asn Pro Val Ser Ala Leu Ser Ala Leu Asp Asn Pro Phe
35 40 45

Arg Ser Ala Asp Asn Ala Thr Gly Arg Ile Thr Ser Ser Ile Gln Pro
50 55 60

Ala Val Gln Cys Ala Ala Ala Ala Ala Thr Glu Gly Ser Cys Pro Arg
65 70 75 80

Gln Ser Pro Cys Ser Gly
85

<210> 39
<211> 111
<212> PRT
<213> Escherichia coli

<400> 39
Met Val Asp Asn Trp Gln Lys Ser Val Arg Ser Arg Ala Leu Pro Glu

```
 1               5                  10                  15

Glu Ala Met Thr Gly Trp Asn Glu Gly Met Ile Arg Leu Gln Gln Leu
            20                  25                  30

Ala Glu Arg Leu Asn Arg Gln Asp Glu Gln Arg Gly Lys Tyr Met Thr
        35                  40                  45

Val Ser Glu Leu Lys Thr Glu Val Phe Gly Ile Met Gln Ala Phe Asn
    50                  55                  60

Arg His Ile Pro Ala Glu Glu Gln Leu Arg Arg Tyr Gly Glu Val Arg
65                  70                  75                  80

Asn Gln Asn Gly Ser Glu Gln Gln Gln Lys Gln Ala Glu Met Ala Leu
                85                  90                  95

Asn Gln Leu Ile Asn Arg Tyr Gln Met Ile Arg Ala Gly Lys Gln
            100                 105                 110
```

<210> 40
<211> 143
<212> PRT
<213> Escherichia coli

<400> 40

```
Met Val Gly Cys Ala Trp Leu Ala Glu Gln Ala Phe Ser Asp His Ala
 1               5                  10                  15

Leu Ser Pro His Ser Ala Trp Pro Tyr Ser Ala Ser Arg Asp Ala Gly
            20                  25                  30

Leu Ala Asp Thr Gly Ala Gly Gly Tyr Pro Thr Cys Lys Gln Arg Trp
        35                  40                  45

Ala Asp Asp Thr Val Gly Leu Lys Ala Arg Leu Leu Gln Leu Pro Ala
    50                  55                  60

Leu Asp Ile Trp Thr Ala Phe Lys Lys Ile Asp Gln Ser Gln Val Val
65                  70                  75                  80

Tyr Glu Glu Ala Val Leu Arg Ser Arg Val Ser Glu Arg Asn Met Gln
                85                  90                  95

Val Ser Gln Asn Gly Arg Val Tyr Pro Ser Tyr Gly Gly Asn Val Asp
            100                 105                 110
```

Gly Thr Val Ala Asn Ala Ala Thr Arg Leu Ala Ser Gly Ala Arg Asn
115 120 125

Ile Leu Gly Ser Ile Ala Ala Cys Thr Ala Phe Asp Ser Val Arg
130 135 140

<210> 41
<211> 118
<212> PRT
<213> Escherichia coli

<400> 41
Met Val Gln Ala Gln Leu Gln Ile Ala Leu Val Ile Cys Ile Pro Leu
1 5 10 15

Ile Thr Leu Cys Ser Ala Trp Asp Val Lys Val Val Met Thr Leu Thr
20 25 30

Phe Val Gln Phe Ala Leu Phe Phe Leu Thr Phe Trp Trp Glu Leu Ala
35 40 45

Arg Trp Leu Asp Ser Trp Leu Leu Asp Val Leu Tyr Asn Ser Asp Thr
50 55 60

His Ser Ser Trp Asn Leu Ala Gly Ile Gln Asn Thr Gln Asp Asp Val
65 70 75 80

Ile Ile Asn Leu Val Met Arg Leu Met Phe Leu Val Leu Pro Thr Phe
85 90 95

Trp Leu Gly Ala Met Thr Trp Ala Gly Val Arg Val Gly Val Ala Leu
100 105 110

Asn Gly Ala Leu Ala Gly
115

<210> 42
<211> 81
<212> PRT
<213> Escherichia coli

<400> 42
Met Lys Tyr Leu Phe Phe Glu Asn Ile His Ser Ile Phe Leu Thr Phe
1 5 10 15

Ser Leu Phe Arg Thr Ser Val Ser Pro Asp Phe Pro Met Ile Phe Ala

20 25 30

Leu Pro Ser Ile Ile Leu Gly Gln Phe Thr Thr Asn Gln Leu Thr Asn
35 40 45

Phe Val Ile Cys Met Gly Asn Thr Val Glu Arg Arg Leu Gly Val Val
50 55 60

His Asn Pro Phe Lys Arg Ser Gly Asp Gly His Asp Leu Arg Ala Val
65 70 75 80

Ala

<210> 43
<211> 348
<212> PRT
<213> Escherichia coli

<400> 43
Leu Ile Val Ile Asp Phe Phe Cys Gly Cys Gly Gly Ala Ser Glu Gly
1 5 10 15

Leu Arg Gln Ala Gly Phe Asp Ile Glu Leu Gly Leu Asp Ile Asp Gln
20 25 30

Gln Ala Ser Glu Thr Phe Lys Ala Asn Phe Pro Asp Ala Lys Phe Ile
35 40 45

Gln Asp Asp Ile Arg Lys Ile Glu Pro Gln Asp Ile Ser Asp Ile Ile
50 55 60

Asp Ile Lys Ala Lys Arg Pro Leu Leu Leu Ser Ala Cys Ala Pro Cys
65 70 75 80

Gln Pro Phe Ser Gln Gln Asn Lys Asn Lys Thr Ser Asp Asp Ser Arg
85 90 95

Arg Asn Leu Leu Asn Glu Thr His Arg Phe Ile Arg Glu Leu Leu Pro
100 105 110

Glu Tyr Ile Met Leu Glu Asn Val Pro Gly Met Gln Lys Ile Asp Glu
115 120 125

Glu Lys Glu Gly Pro Phe Gln Glu Phe Ile Lys Leu Leu Lys Glu Leu
130 135 140

Glu Tyr Asn Tyr Ile Ser Phe Ile Ala Asn Ala Glu Asn Tyr Gly Ile

145 150 155 160

Pro Gln Arg Arg Lys Arg Leu Val Leu Leu Ala Ser Arg Val Gly Lys
165 170 175

Val Thr Leu Pro Glu Ile Thr His Gly Lys Asn Lys Ile Pro Phe Lys
180 185 190

Thr Val Arg Asp Tyr Ile Gln Asp Phe Thr Lys Leu Cys Ser Gly Glu
195 200 205

Thr Asp Pro Lys Asp Pro Leu His Arg Ala Gly Thr Leu Ser Pro Leu
210 215 220

Asn Leu Lys Arg Ile Met His Thr Pro Glu Gly Gly Asp Arg Arg Asn
225 230 235 240

Trp Pro Glu Glu Leu Val Asn Lys Cys His Lys Asn Tyr Asp Gly His
245 250 255

Thr Asp Thr Tyr Gly Arg Met Ser Trp Asp Lys Pro Ala Pro Thr Leu
260 265 270

Thr Thr Lys Cys Asn Ser Tyr Ser Asn Gly Arg Phe Gly His Pro Asp
275 280 285

Pro Thr Gln His Arg Ala Ile Ser Ile Arg Glu Ala Ser Arg Leu Gln
290 295 300

Thr Phe Pro Leu Ser Tyr Val Phe Lys Gly Ser Leu Asn Ser Met Ala
305 310 315 320

Lys Gln Ile Gly Asn Ala Val Pro Cys Glu Leu Ala Arg Leu Phe Gly
325 330 335

Leu His Leu Ile Glu Asn Cys Thr Asn Lys Asp Ser
340 345

<210> 44
<211> 974
<212> PRT
<213> Escherichia coli

<400> 44
Met Leu Gly Arg Gln Gln Ile Ala Gly Ile Pro Thr Ala Leu Ser Glu
1 5 10 15

```
Leu Phe Lys Asn Ala His Asp Ala Tyr Ala Asp Asn Val Glu Val Asp
            20                  25                  30

Phe Phe Arg Lys Glu Asn Leu Leu Ile Leu Arg Asp Asp Gly Leu Gly
        35                  40                  45

Met Thr Thr Asp Glu Phe Glu Glu Arg Trp Leu Thr Ile Gly Thr Ser
    50                  55                  60

Ser Lys Leu Ile Asp Asp Asp Ala Ile Asn Lys Pro Ala Val Asp Ser
65                  70                  75                  80

Asn Lys Ala Phe Arg Pro Ile Met Gly Glu Lys Gly Ile Gly Arg Leu
                85                  90                  95

Ser Ile Ala Ala Ile Gly Pro Gln Val Leu Val Leu Thr Arg Ala Lys
            100                 105                 110

Arg Asp Asn Glu Leu Lys Pro Leu Val Ala Ala Phe Val Asn Trp Ser
        115                 120                 125

Leu Phe Ala Ile Pro Ser Leu Asp Leu Asp Asp Ile Glu Ile Pro Ile
    130                 135                 140

Arg Thr Ile Ile Asn Asp Glu Cys Phe Thr Lys Lys Thr Leu Asp Glu
145                 150                 155                 160

Met Ile Glu Gln Ala Arg Asn Asn Leu Asp Ser Leu Ser His Lys Ile
                165                 170                 175

Ser Lys Ser Lys Val Ser Gln Ile Asn Thr Gln Leu Ser Ser Phe Glu
            180                 185                 190

Phe Asp Pro Ile Leu Trp Glu Lys Lys Leu Gly Gly Leu Arg Leu Ser
        195                 200                 205

Gly Asp Gly His Gly Thr His Phe Ile Ile Met Pro Thr Glu Glu Ile
    210                 215                 220

Leu Ile Asp Asp Ile Ser Thr Ser Asp Ser Asn Lys Thr Ser Glu Gln
225                 230                 235                 240

Ser Ser Arg Leu Glu Lys Ala Leu Leu Gly Phe Thr Asn Thr Met Tyr
                245                 250                 255

Ser Asp Ser Asn Pro Pro Ile Ile Ala Arg Phe Arg Asp Tyr Leu Glu
            260                 265                 270
```

```
Asp Gly Glu Cys Ile Asp Arg Ile Ser Glu Ser Ile Phe Phe Thr Pro
        275                 280                 285

Gln Glu Phe Asn Leu Ala Asp His His Ile Glu Gly Trp Phe Asn Glu
    290                 295                 300

Phe Gly Gln Phe Ser Gly Thr Val Ser Val Tyr Gly Glu Glu Pro Ile
305                 310                 315                 320

His His Val Val Thr Trp Lys Asn Asn Asn Gln Leu Thr Gln Cys Gly
                325                 330                 335

Pro Phe Lys Ile Lys Leu Ala Tyr Ile His Gly Arg Leu Arg Asp Ser
            340                 345                 350

Arg Leu Pro Met Glu Leu Trp Ala Pro Leu Lys Glu Lys Thr Asp Arg
        355                 360                 365

Tyr Gly Gly Leu Tyr Ile Tyr Arg Asp Gly Leu Arg Ile Leu Pro Tyr
    370                 375                 380

Gly Asp Ser Asp Thr Asp Phe Leu Lys Ile Glu Lys Arg Arg Thr Leu
385                 390                 395                 400

Ser Ala Ser Glu Tyr Phe Phe Ser Tyr Arg Arg Leu Phe Gly Ala Ile
                405                 410                 415

Glu Leu Thr Lys Glu Asn Asn Ala Ser Leu Val Glu Lys Ala Gly Arg
            420                 425                 430

Glu Gly Phe Ile Glu Asn Lys Pro Tyr Lys Gln Phe Lys Glu Met Leu
        435                 440                 445

Glu Asn Phe Phe Ile Glu Ile Ala Arg Asp Phe Phe Lys Asp Asp Gly
    450                 455                 460

Asp Met Ser Glu Leu Phe Val Glu Thr Lys Gln Arg Arg Asn Glu Glu
465                 470                 475                 480

His Asp Leu Leu Ser Lys Arg Ser Lys Gln Thr Lys Ala Lys Lys Asp
                485                 490                 495

Arg Leu Lys Lys Asp Leu Tyr Asp Phe Phe Asp Lys Leu Asp Asn Asp
            500                 505                 510

Tyr Trp Asn Ile Glu Ile Asn Lys Leu Ile Asn Lys Asn Glu Glu Tyr
        515                 520                 525
```

```
Phe Ser Ser Thr Glu Ile Thr Asp Thr Asn Ile Asp Tyr Val Tyr Asn
    530                 535                 540

Lys Ile Lys Glu Gln Asn Asp Ala Ile Ile Lys Asn Leu Arg Asn Ser
545                 550                 555                 560

Val Asp Ile Lys Lys Pro Ser Gly Val Gly Leu Thr Lys Glu Leu Ser
                565                 570                 575

Asn Leu Trp Asp Arg Tyr Gln Ile Glu Arg Gln Lys Ile Leu Leu Ser
            580                 585                 590

Leu Asn Glu Leu Lys Asp Asn Val Asp Arg Lys Leu Ile Glu Leu Asp
        595                 600                 605

Asn Lys Asn Asn Asp Phe Leu Asn Leu Arg Lys Arg Leu Glu Asp Ser
    610                 615                 620

Leu Asn Leu Gln Gln Ser Tyr Tyr Glu Lys Glu Leu Thr Lys Leu Tyr
625                 630                 635                 640

Asn Asp Ala Lys Asn Ala Leu Lys Asp Val Gln Ser Lys Ala Asn Arg
                645                 650                 655

Leu Ile Ser Asp Asn Lys Lys Lys His Lys Ser Glu Leu Lys Asn Ile
            660                 665                 670

Ser Tyr Glu Phe Gln Ser Thr Asn Leu Asn Gly Lys Asp Thr Ala Tyr
        675                 680                 685

Ile Leu Asp Val Lys Arg Asn Leu Glu Ser Lys Ile Glu Asn Thr Ser
    690                 695                 700

Asn Glu Val Ile Asn Glu Ile Arg Lys Leu Thr Asp Gln Ile Ala Ile
705                 710                 715                 720

Ile Ser Asp Ser Thr Thr Ser Glu Asn Leu Ser Ser Ala Gln Val Thr
                725                 730                 735

Glu Ala Ile Glu Thr Glu Leu Glu His Leu Arg Asp Gln Gln Ala Asn
            740                 745                 750

Asn Ala Glu Leu Ile Leu Leu Gly Met Ala Leu Ser Val Val His His
        755                 760                 765

Glu Phe Asn Gly Asn Ile Arg Ala Ile Arg Ser Ala Leu Arg Glu Leu
    770                 775                 780
```

```
Lys Ala Trp Ala Asp Arg Asn Pro Lys Leu Asp Ile Ile Tyr Gln Lys
785                 790                 795                 800

Ile Arg Thr Ser Phe Asp His Leu Asp Gly Tyr Leu Lys Thr Phe Thr
                805                 810                 815

Pro Leu Thr Arg Arg Leu Ser Arg Ser Lys Thr Asn Ile Thr Gly Thr
            820                 825                 830

Ala Ile Leu Glu Phe Ile Arg Asp Val Phe Asp Asp Arg Leu Glu Lys
        835                 840                 845

Glu Gly Ile Glu Leu Phe Thr Thr Ser Lys Phe Val Asn Gln Glu Ile
    850                 855                 860

Val Thr Tyr Thr Ser Thr Ile Tyr Pro Val Phe Ile Asn Leu Ile Asp
865                 870                 875                 880

Asn Ala Ile Tyr Trp Leu Gly Lys Thr Thr Gly Glu Lys Arg Leu Ile
                885                 890                 895

Leu Asp Ala Thr Glu Thr Gly Phe Val Ile Gly Asp Thr Gly Pro Gly
            900                 905                 910

Val Ser Thr Arg Asp Arg Asp Ile Ile Phe Asp Met Gly Phe Thr Arg
        915                 920                 925

Lys Thr Gly Gly Arg Gly Met Gly Leu Phe Ile Ser Lys Glu Cys Leu
    930                 935                 940

Ser Arg Asp Gly Phe Thr Ile Arg Leu Asp Asp Tyr Thr Pro Glu Gln
945                 950                 955                 960

Gly Ala Phe Phe Ile Ile Glu Pro Ser Glu Glu Thr Ser Glu
                965                 970
```

<210> 45
<211> 555
<212> PRT
<213> Escherichia coli

<400> 45

```
Met Thr Ser Ser Thr Asp Phe His Lys Leu Ser Glu Asp Cys Val Arg
  1               5                  10                  15

Arg Phe Leu His Ser Val Val Ala Val Asp Asp Asn Met Ser Phe Gly
            20                  25                  30
```

Ala Gly Ser Asp Thr Phe Pro Thr Asp Glu Asp Ile Asn Ala Leu Val
35 40 45

Asp Pro Asp Asp Asp Pro Thr Pro Ile Ile Thr Ala Ser Ala Ser Pro
50 55 60

Arg Ile Glu Ser Thr Lys Ser Lys Ala Lys Val Lys Asn His Pro Phe
65 70 75 80

Asp Tyr Gln Ala Leu Ala Glu Ala Phe Ala Lys Asp Gly Ile Ala Cys
85 90 95

Cys Gly Leu Leu Ala Lys Ser Phe Asn Val Glu Glu Arg Asp Ile Ile
100 105 110

Thr Ala Ser Ser His Lys Ala Asp Ile Thr Ile Leu Asp Trp Asp Met
115 120 125

Gln Ser Asp Ser Gly Gln Phe Ala Ile Glu Ile Ile Lys Ser Ile Ile
130 135 140

Val Ser Asp Ile Asn Ser Gly Gly Arg Leu Arg Leu Leu Ser Ile Tyr
145 150 155 160

Thr Gly Glu His Val Thr Ala Val Ile Thr Lys Leu Asn Asn Glu Leu
165 170 175

Lys Lys Thr Tyr Arg Ser Val Ile Lys Asn Asp Asp Ser Ile Phe Ile
180 185 190

Glu Asp Asn Tyr Ala Leu Glu Gln Trp Cys Ile Val Val Ile Ser Lys
195 200 205

Asp Val Tyr Glu Lys Asp Leu Pro Asn Val Leu Ile Lys Lys Phe Thr
210 215 220

Asn Leu Thr Ala Gly Leu Leu Ser Asn Ala Ala Leu Ser Cys Ile Ser
225 230 235 240

Glu Ile Arg Glu Lys Thr His Gly Ile Leu Thr Lys Tyr Asn Asn Lys
245 250 255

Leu Asp Thr Ala Tyr Val Ser His Ile Leu Asn Leu Ile Lys Ser Lys
260 265 270

Glu Ser Arg Ala Tyr Ala Tyr Glu Asn Ala His Asp Tyr Ala Val Asp
275 280 285

```
Leu Ile Ser Glu Glu Ile Arg Ser Ile Leu Gln Ile Ser Glu Asn Leu
    290                 295                 300

Lys Lys Ser Leu Ser Lys Asn Ser Leu Ser His Trp Pro Ile Phe His
305                 310                 315                 320

Tyr Ala Lys Asn Gly Cys Lys Asn Phe Leu Leu Thr Gly Lys Lys Gln
                325                 330                 335

Lys Asp Leu Ser Val Glu His Leu Arg Asn Ile Leu Ser Ala Asp Ser
            340                 345                 350

Leu Glu Glu Ile Gln His Ala Ile Glu His Ala Ser Leu Gly Lys Lys
        355                 360                 365

Glu Tyr Leu Ser Gln Asp Gly Glu Glu Asp Lys Lys Leu Met Gln Leu
    370                 375                 380

Cys Ser Leu Glu Ile Thr Arg Arg Ser Leu Arg Tyr His Ser His Ile
385                 390                 395                 400

Asp Asn Val Ser Leu Lys Gln Gly Thr Leu Leu Leu Asp Ala Tyr Asn
                405                 410                 415

Phe Val Tyr Leu Cys Ile Gln Pro Leu Cys Asp Ser Val Arg Leu His
            420                 425                 430

Glu Lys Ala Asp Phe Leu Phe Leu Arg Gly Thr Leu Asp Asp Asn Asn
        435                 440                 445

Tyr Asn Leu Leu Ile Glu Asp Glu Tyr Gly Gly Phe Tyr Lys Ile Lys
    450                 455                 460

Met Pro Ala Lys Ala Ser Asn Ile Ile Ser Phe Ser Phe Gly Val Glu
465                 470                 475                 480

Asn Gly Asn Gly Val Ile Ile Gly Lys Lys Asn Asn Leu Val Asn Thr
                485                 490                 495

Asp Tyr Ile Ser Phe Val Pro Leu Leu Val Glu Lys Ile Ser Thr Pro
            500                 505                 510

Lys Val Leu Lys Trp Ile Gly Glu Ile Lys Thr Thr Tyr Ala Gln Lys
        515                 520                 525

Ile Thr Thr Asp Ile Val Ala Asn Leu Ser Arg Ile Gly Leu Asp Gln
    530                 535                 540
```

His Glu Trp Leu Arg Ile Lys Ser Lys Asp Ile
545 550 555

<210> 46
<211> 82
<212> PRT
<213> Escherichia coli

<400> 46
Met Ser Ser Arg Gln Ile Leu Glu His Tyr Asn Ala Leu Thr Tyr Pro
1 5 10 15

Leu His Gln Ser Ile Leu Leu Gln Ile Met Thr Ser Asn Leu Leu Ser
20 25 30

Val Cys Thr Gly Lys Ser Ile Tyr Glu Asp Ile Ser Gly Ser Ser Trp
35 40 45

Asn Ile Ile His Phe Asn Ile Pro Leu Pro Ile Ser Arg Ala Arg Leu
50 55 60

Ser Ile Phe Ser Tyr Cys Val Arg Ile Lys Pro Trp Met Ser Met Asp
65 70 75 80

Tyr Met

<210> 47
<211> 98
<212> PRT
<213> Escherichia coli

<400> 47
Met Ser Ile Ile Phe Asn Gly His Tyr Arg Met Lys His Arg Thr Trp
1 5 10 15

Ile Thr Glu Ala Leu Arg Leu His Phe Glu Glu His Leu Pro Gln Val
20 25 30

Val Val Gly Arg Arg Leu Gly Val Pro Lys Ser Thr Ala Cys Gly Met
35 40 45

Phe Val Arg Phe Arg Lys Ala Gly Phe Ser Trp Pro Leu Pro Ala Gly
50 55 60

Met Ser Glu Arg Glu Leu Asp Gly Arg Leu Tyr Gly Ser Thr Ser Thr

65 70 75 80

Val Pro Val Val Leu Cys Ser Gly Ser Val Ile Gln Asp Thr Ser Lys
85 90 95

Ser Cys

<210> 48
<211> 106
<212> PRT
<213> Escherichia coli

<400> 48
Met Ile Lys Thr Arg Arg Thr Lys Arg Thr Phe Ser Pro Glu Phe Lys
1 5 10 15

Leu Glu Ala Phe Glu Gln Val Val Val Lys Tyr Gln Arg Asp Val Arg
20 25 30

Glu Val Ala Gln Ala Leu Glu Leu Asn Pro Asp His Leu Arg Lys Trp
35 40 45

Ile Arg Leu Tyr Lys Gln Glu Leu Gln Gly Ile Glu Pro Ala Gly Asn
50 55 60

Ala Ile Thr Pro Glu Gln Arg Glu Ile Gln Gln Leu Lys Ala Gln Ile
65 70 75 80

Lys Arg Val Glu Met Glu Lys Glu Ile Leu Lys Gln Ala Ala Val Leu
85 90 95

Met Ser Glu Ile Pro Gly Lys Leu Ser Arg
100 105

<210> 49
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 49
tgctctagag ccattactca gaatggg 27

<210> 50
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 50
cgcgagctcg acgactgaat gatccc 26

<210> 51
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 51
tcccccgggt actgcagcac tcaacc 26

<210> 52
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 52
gatcccggga ccactgaaat gcgtgc 26

<210> 53
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 53
tcgtctagag atgatggtga tggagcg 27

<210> 54
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 54
gaactgcagc caaatactga taccaccc 28

<210> 55
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 55
gaactgcagg ctaaaacaga agacgcg 27

<210> 56
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 56
catgcatgca ctccatatga caaccgc 27

<210> 57
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 57
tcgtctagaa tgaagctgcg catgagg 27

<210> 58
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 58
caactgcagt cgcaaattgc gaactgg 27

<210> 59
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 59
caactgcaga ccgcaacttt tcgacgc 27

<210> 60
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 60
catgcatgcc agtgagccat tgttccc 27

<210> 61
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 61
tgctctagat acgactctga caggagg 27

<210> 62
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 62
tcagatatca actaccagca gtttgg 26

<210> 63
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 63
tcagatatcc ataaagagtg acgtggc 27

<210> 64
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 64
tgctctagaa aacgtggcaa cagagcg 27

<210> 65
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 65
tgctctagaa ggcgttgtcg atcctg 26

<210> 66
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 66
gaactgcagg aaaaggccga gcagactg 28

<210> 67
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 67
gaactgcagt acagccatgt ttacggt 27

<210> 68
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 68
catgcatgcg gtgtacgaca gtttgcg 27

<210> 69
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 69
tgctctagac acatcatggg cacacc 26

<210> 70
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 70
gaactgcaga accgtccaca tcaggcg 27

<210> 71
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 71
gaactgcaga ccctgcttgc cattccg 27

<210> 72
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Oligonucleotide

<400> 72
catgcatgca taagcgtcga acaggcg 27